FILE HISTORY

US 6,713,464

PATENT:	6,713,464
INVENTORS:	Meese, Claus
	Sparf, Bengt
TITLE:	Derivatives of 3,3-diphenylpropylamines
APPLICATION NO:	US2000700094A
FILED:	02 JAN 2001
ISSUED:	30 MAR 2004
COMPILED:	17 SEP 2013

ISSUE CLASSIFICATION	Class	Subclass
	514	175

FILED UNDER 35 U.S.C. 371

PATENT NUMBER

6713464

6713464

U.S. UTILITY PATENT APPLICATION

O.I.P.E.

SCANNED AK (2) Q.A. VB

PATENT DATE

MAR 3 0 2004

APPLICATION NO.	CONT/PRIOR	CLASS	SUBCLASS	ART UNIT	EXAMINER
09/700094	D F	514	175	1614	1

APPLICANTS

Claus Nerenz
Bernd Sperl

TITLE

Derivatives of 4-diphenylmethylpiperazine
(as amended per Examiner)

PTO-2040
12/99

PREPARED AND APPROVED FOR ISSUE

ISSUING CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					
514	175	514	529	530	546	547	548	
INTERNATIONAL CLASSIFICATION		549	269					
A61K	31/215	560	140	255				
A01N	37/08	564	316					
A61N	37/02							
A61K	31/22							
A61K	31/225			☐ Continued on Issue Slip Inside File Jacket				

2-20-04 Formal Drawings (1 sheet) rec'd 4.25.03

DRAWINGS			CLAIMS ALLOWED	
Sheets Drwg.	Figs. Drwg.	Print Fig.	Total Claims	Print Claim for O.G.
ONE	ONE	ONE	26	1

(ZACHARY C. TULKER) 29 OCT. '03
(Assistant Examiner) (Date)

JOHN M. FORD
PRIMARY EXAMINER
GROUP ART UNIT
(Primary Examiner) (Date)

(Legal Instruments Examiner) (Date)

NOTICE OF ALLOWANCE MAILED

11-06-03

ISSUE FEE

Amount Due	Date Paid
1,330.	1-28-04

ISSUE BATCH NUMBER

☐ a) subseq has be

☐ b) not ext of U.S

☐ c) this pa

O.G.

D

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Form PTO
(Rev. 6/98)

ISSUE FEE IN FILE

(LABEL AREA)

(FACE)

6,713,464

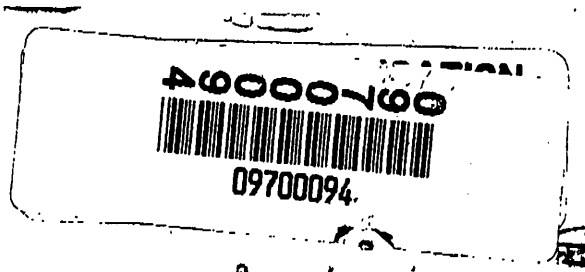
NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Transaction History

Date	Transaction Description
11/8/2000	Receipt of 371 Request
11/17/2000	371 Application Preexamination Docketing
11/17/2000	Correspondence Address Change
12/4/2000	371 Application Preexamination Docketing
12/5/2000	Notice of DO/EO Missing Requirements Mailed
1/2/2001	Preliminary Amendment
1/2/2001	Affidavit(s) (Rule 131 or 132) or Exhibit(s) Received
1/2/2001	Applicant 371 Filing Paper Received
1/2/2001	Applicant 371 Filing Paper Received
1/2/2001	Initial Exam Team nn
1/16/2001	Released to OIPE
1/16/2001	Notice of DO/EO Acceptance Mailed
1/30/2001	IFW Scan & PACR Auto Security Review
2/15/2001	Application Dispatched from OIPE
5/2/2001	Case Docketed to Examiner in GAU
6/27/2001	Change in Power of Attorney (May Include Associate POA)
6/27/2001	Correspondence Address Change
6/27/2001	Change in Power of Attorney (May Include Associate POA)
8/15/2001	Information Disclosure Statement (IDS) Filed
8/15/2001	Information Disclosure Statement (IDS) Filed
9/7/2001	Mail Restriction Requirement
9/7/2001	Restriction/Election Requirement
4/9/2002	Case Docketed to Examiner in GAU
4/10/2002	Mail Abandonment for Failure to Respond to Office Action
4/10/2002	Aband. for Failure to Respond to O. A.
5/31/2002	Petition Entered
1/17/2003	Response to Election / Restriction Filed
1/17/2003	Request for Extension of Time - Granted
1/17/2003	Mail-Petition to Revive Application - Granted
1/24/2003	Mail Notice of Rescinded Abandonment
1/24/2003	Notice of Rescinded Abandonment in TCs
2/6/2003	Mail Non-Final Rejection
2/6/2003	Non-Final Rejection

2/6/2003	Date Forwarded to Examiner
2/6/2003	Correspondence Address Change
4/14/2003	Response after Non-Final Action
4/24/2003	Date Forwarded to Examiner
4/28/2003	Workflow - Drawings Finished
4/28/2003	Workflow - Drawings Matched with File at Contractor
4/28/2003	Supplemental Response
5/8/2003	Date Forwarded to Examiner
5/15/2003	Notice of Allowance Data Verification Completed
5/15/2003	Case Docketed to Examiner in GAU
5/16/2003	Mail Notice of Allowance
5/19/2003	Dispatch to Publications
5/22/2003	Workflow - File Sent to Contractor
5/22/2003	Receipt into Pubs
7/11/2003	Receipt into Pubs
8/18/2003	Information Disclosure Statement (IDS) Filed
8/18/2003	Information Disclosure Statement (IDS) Filed
8/18/2003	Request for Continued Examination (RCE)
8/18/2003	Workflow - Request for RCE - Finish
8/18/2003	Workflow - Request for RCE - Begin
10/28/2003	Date Forwarded to Examiner
10/28/2003	Disposal for a RCE / CPA / R129
11/3/2003	Formal Drawings Required
11/3/2003	Notice of Allowance Data Verification Completed
11/4/2003	Mail Notice of Allowance
11/4/2003	Mail Formal Drawings Required
12/10/2003	Receipt into Pubs
1/28/2004	Issue Fee Payment Verified
1/28/2004	Issue Fee Payment Received
2/18/2004	Correspondence Address Change
2/20/2004	Application Is Considered Ready for Issue
2/25/2004	Receipt into Pubs
3/11/2004	Issue Notification Mailed
3/30/2004	Patent Issue Date Used in PTA Calculation
4/6/2004	Recordation of Patent Grant Mailed
4/20/2004	Correspondence Address Change
2/28/2005	Post Issue Communication - Certificate of Correction
3/7/2006	Correspondence Address Change
3/8/2006	Change in Power of Attorney (May Include Associate POA)

09/700094



EP99/03212

INITIALS

CONTENTS

	Date received (Incl. C. of M.) or Date Mailed		Date received (Incl. C. of M.) or Date Mailed
1. Application papers.		42.	
2. 905	08 DEC 2000	43.	
3. del 903	2Jan01	44.	
4.	16 JAN 2001	45.	
5. IDS	11-8-01	46.	
6. Rce-Amdt A	12-2-01	47.	
7. P/A	4-24-01	48.	
8. Notification P/A Accepted	6-27-01	49.	
9. IDS	8-15-01	50.	
10. Restriction	9/7/01	51.	
11. abandonment	4/10/02	52.	
12. Petition Revival Amdt B	5-21-02	53.	
13. Pet- Granted	1-17-03	54.	
14. Change of address	1/28/03	55.	
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16. Amdt C	4/4/03	57.	
17. Supp Amdt D	4/28/03	58.	
18. EXAMINER'S AMDT E ET	5/16/03	59.	
19. Allowance	5/16/03	60.	
20. RCE	8/18/03	61.	
21. Suppl IDS	8/18/03	62.	
22. Allowability	11-4-3	63.	
23. Allowance	11-4-3	64.	
24. Add Chgs	1/26/04	65.	
25.	1/31/05	66.	
26.		67.	
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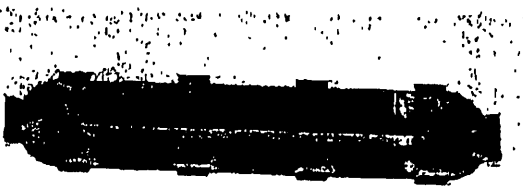

SEARCHED

Class	Sub.	Date	Exmr.
560	110, 108, 121, 123, 124, 138, 140, 142	1/28/03	ZT
514	530, 531, 532, 533, 534, 544, 547, 548, 551		
UPDATE:			
549	269	4/28/03	ZT
514	175, 529, 530, 547, 548		
560	140, 255		
564	316 (MAINS)		
RCE:			
549	269	10/29/03	ZT
514	175, 529, 530, 547, 548		
560	140, 255		
564	316		

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
549	269	8/12/03	ZT
514	175, 529, 530, 547, 548		
560	140, 255		
564	316		

SEARCH NOTES (INCLUDING SEARCH STRATEGY)

	Date	Exmr.
STN REGISTRY CAPLUS STRUCTURE - ESTERS x w/ CAPLUS. (TRANSCRIPT ATTACHED)	1/28/03	ZT
EAST USPAT DERWENT EPO JPO USPG PUB "TOLTERODINE" "METABOLITE".	1/28/03	ZT
CAN M INVENTOR SEARCH -	1/28/03	ZT
UPDATE: EAST - USPAT - X w/ SUBCLASSES EPO, JPO, DERWENT "TOLTERODINE"	4/28/03	ZT

(RIGHT OUTSIDE)

US006713464B1

(12) **United States Patent**
Meese et al.

(10) **Patent No.: US 6,713,464 B1**
(45) **Date of Patent: Mar. 30, 2004**

(54) **DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**

(75) Inventors: **Claus Meese**, Monheim (DE); **Bengt Sparf**, Trangsund (SE)

(73) Assignee: **Schwarz Pharma AG**, Monheim (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/700,094**

(22) PCT Filed: **May 11, 1999**

(86) PCT No.: **PCT/EP99/03212**

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(2), (4) Date: **Jan. 2, 2001**

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(30) **Foreign Application Priority Data**

May 12, 1998 (EP) 98108608

(51) **Int. Cl.**[7] **A61K 31/215**; A61K 31/22; A61K 31/225; A01N 37/08; A01N 37/02

(52) **U.S. Cl.** **514/175**; 514/529; 514/530; 514/546; 514/547; 514/548; 549/269; 560/140; 560/255; 564/316

(58) **Field of Search** 560/110, 108, 560/121, 123, 124, 138, 140, 142, 255; 514/530, 531, 532, 533, 534, 544, 547, 548, 551, 175, 529; 549/269; 564/316

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,313,132 B1 11/2001 Johansson et al. 514/277

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WO WO 89/06644 7/1989
WO WO 94/11337 * 5/1994

OTHER PUBLICATIONS

Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU–200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology, vol. 81, pp. 169–172 (1997).*

Nilvebrant et al, "Tolterodine—A New Bladder Selective Muscarinic Receptor Antagonist: Preclinical Pharmacological and Clinical Data" Life Sciences, vol. 60(13/14), pp. 1129–1136 (1997).*

Postlind et al, "Tolterodine, A New Muscarinic Receptor Antagonist, is Metabolized by Cytochromes P450 and 3A in Human Liver Microsomes" Drug Metabolism and Disposition, vol. 26(4), pp. 289–293 (1998).*

Andersson et al, "Biotransformation of Tolterodine, A New Muscarinic Receptor Antagonist, in Mice, Rats, and Dogs" Drug Metabolism and Disposition, vol. 26(6), pp. 528–535 (1998).*

Brynne et al, "Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity" J. Clin. Pharm. Ther. vol. 35(7), pp. 287–295 (1997).*

Nilvebrant et al., *European Journal of Pharmacology*, 327(1997) pp. 195–207.

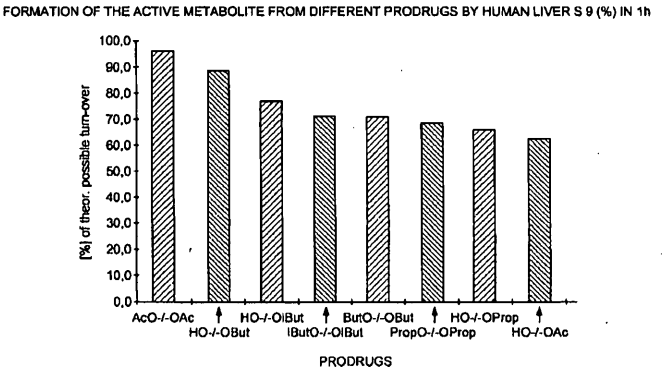
* cited by examiner

Primary Examiner—John M. Ford
Assistant Examiner—Zachary C. Tucker
(74) *Attorney, Agent, or Firm*—Edwards & Angell, LLP; Peter F. Corless; Christine C. O'Day

(57) **ABSTRACT**

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of anti-muscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

26 Claims, 1 Drawing Sheet



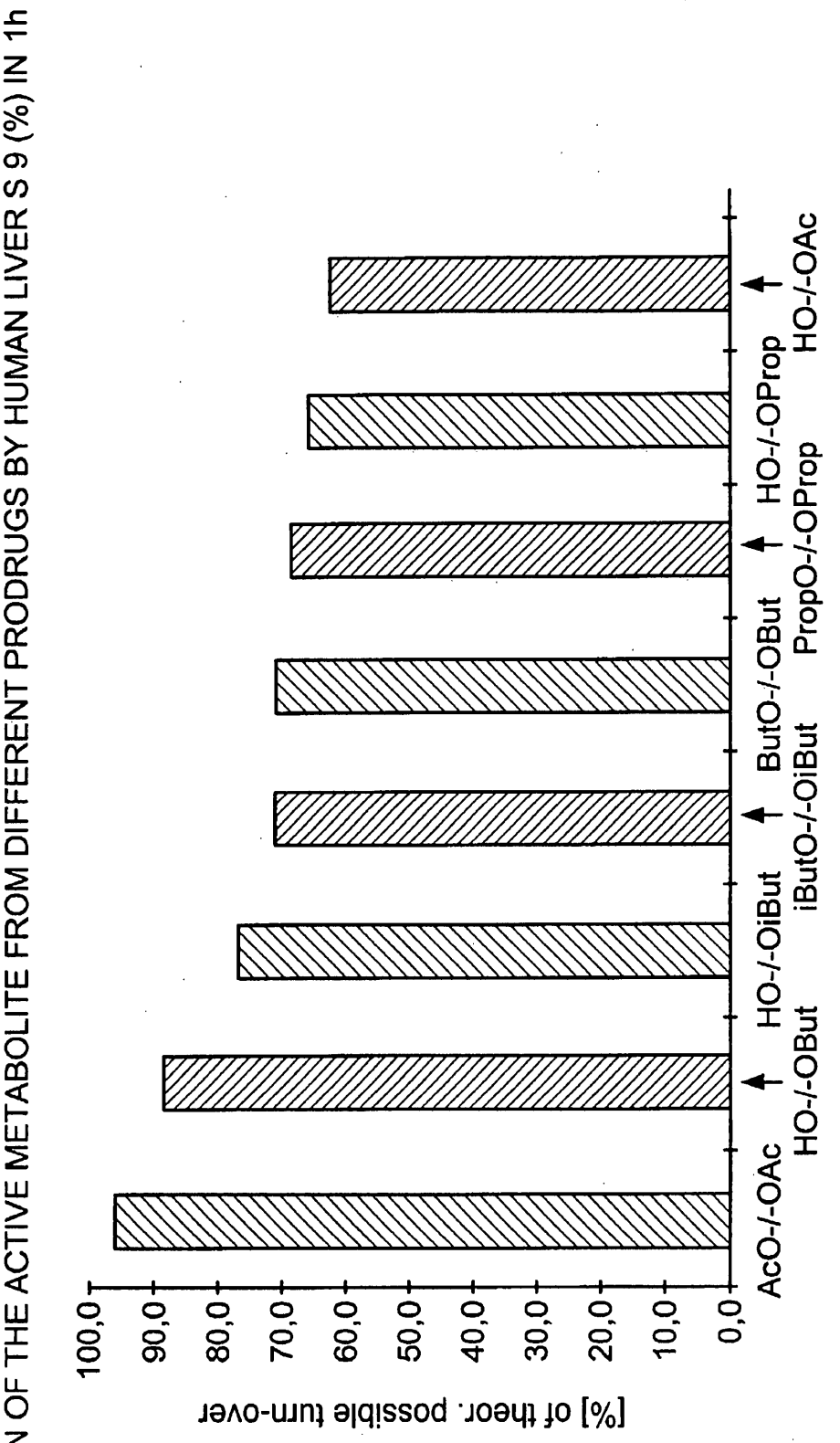

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h
[%] of theor. possible turn-over
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
AcO-/-OAc
HO-/-OBut
HO-/-OiBut
iButO-/-OiBut
ButO-/-OBut
PropO-/-OProp
HO-/-OProp
HO-/-OAc
PRODRUGS

FIG.1

DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

BACKGROUND OF THE INVENTION

The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, Urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to result in poor compliance or discontinuation of Treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477–494; Kelleher et al. 1994).

Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine—a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195–207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195–207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage compared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic

side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

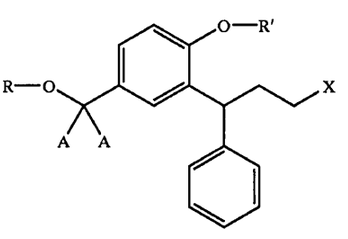
BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the formation of the active metabolite from different prodrugs by human liver S 9(%) in 1 hour.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, novel 3,3-diphenylpropyl amines are provided, which are represented by the general formulae I and VII'

Formula I



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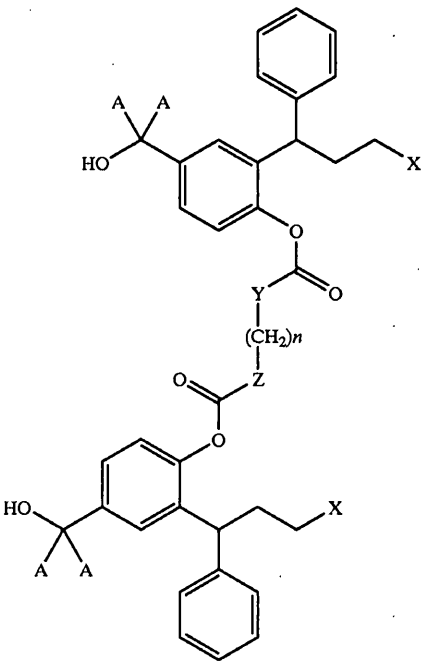
Formula VII'



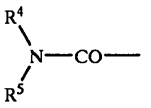
wherein R and R' are independently selected from

a) hydrogen, C_1–C_6 alkyl, C_3–C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1–C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

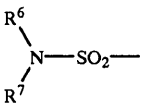
c) C_1–C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)



wherein R^4 and R^5 independently represent hydrogen, C_1–C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e)



wherein R^6 and R^7 independently represent C_1–C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

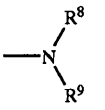
f) an ester moiety of inorganic acids,

g) —$SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1–C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia

Formula Ia



wherein R^8 and R^9 represent non-aromatic hydrocaryl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12 and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

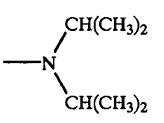
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as $C_{1\text{-}8}$-alkyl, especially $C_{1\text{-}5}$-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

According to another embodiment of the invention, at least one of R^8 *and* R^9 comprises a branched carbon chain.

Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

a)



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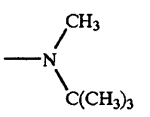

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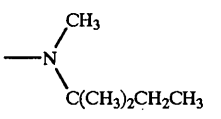
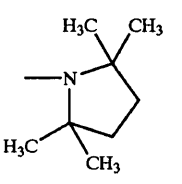


d)



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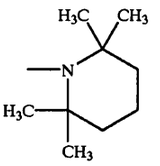
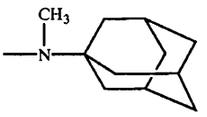
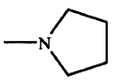
e)



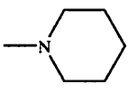
f)



g)



h)



Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benyl group $—CH_2—C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1–C_6 alkylcarbonyl" denotes a group R—C(=O)— wherein R is an alkyl group as defined hereinbefore. Preferred C_1–C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R—C(=O)— wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl-(C_6H_5—), naphthyl-($C_{10}H_7$—), anthryl-($C_{14}H_9$—), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula $—CO—C_6H_5$ wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and nitro. As substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1–C_6 alkoxycarbonyl" refers to a group ROC(=O)— wherein R is an alkyl group as defined hereinbefore. Preferred C_1–C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)—$, $C_2H_5—OC(=O)—$, $C_3H_7OC(=O)—$ and $(CH_3)_3COC(=O)—$ and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$, or $C_n(H_2O)_n$ and corresponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

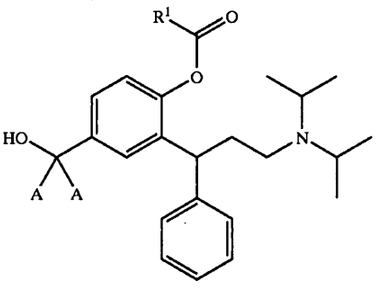
The term "Bn" as used herein denotes a benzyl group.

Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the genera formulae II and II'

Formula II



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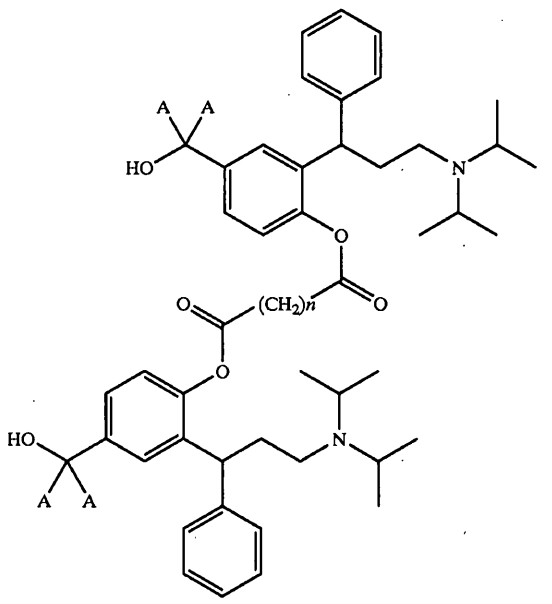
Formula II'



wherein R^1 represents hydrogen, C_1–C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

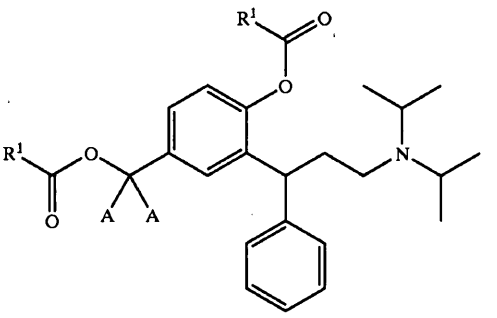
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula

Formula III



wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,

(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,

(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,

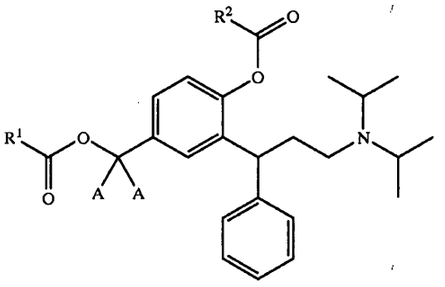
cyclic oct-4-ene-1,8-dioate of Intermediate B,

cyclic octane-1,8-dioate of Intermediate B,

poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV

Formula IV



wherein R^1 is as defined above and

R represents hydrogen, C_1–C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,

(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

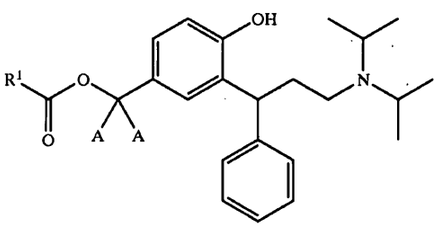
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V

Formula V



wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

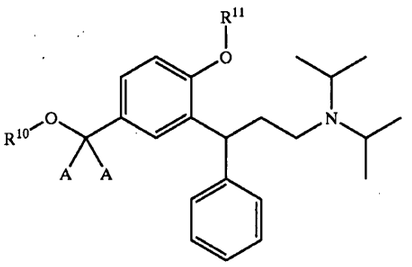
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI

Formula VI



wherein at least one of R^{10} and R^{11} is selected from C_1–C_6 alkyl, benzyl or —$SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1–C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,

(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,

(±)-diisopropyl-[3-(5-methoxymethyl-2-trimehylsilanyloxyphenyl)-3-phenylpropylamine,

(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,

(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,

(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,

(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,

(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,

(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,

(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

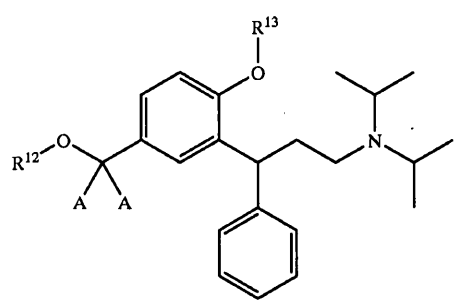
(±)-benzoic acid 4-benzyloxy-3-(3-d4isopropylamino-1-phenylpropyl)-benzyl ester,

(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

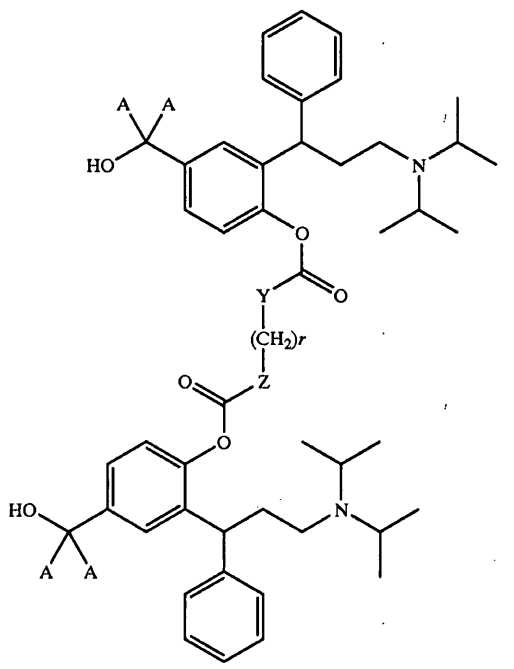
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

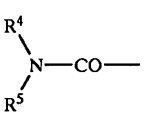
Formula VII



Formula VIII



wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1–C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

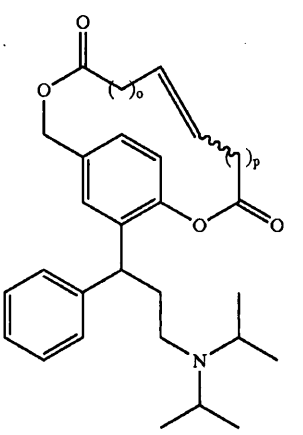
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'

Formula IX



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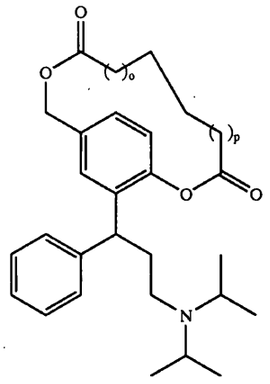
Formula IX'

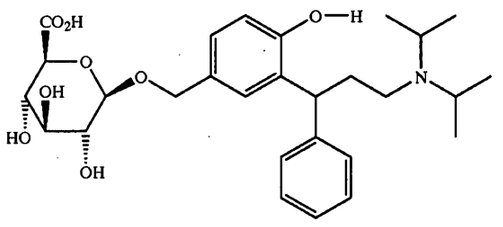


wherein o and p are the same or different and represent the number of methylene units $-(CH_2)-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylaminophenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



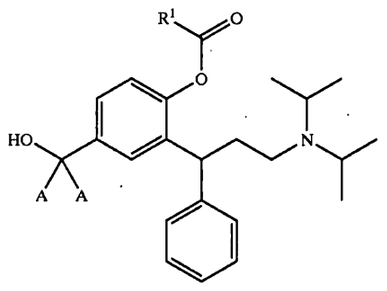
and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

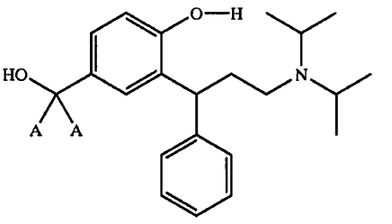
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, he following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II

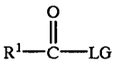
Formula II



as defined above, which comprises treatment of a compound of the formula

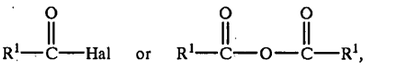


with an equivalent of an acylating agent selected from



wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

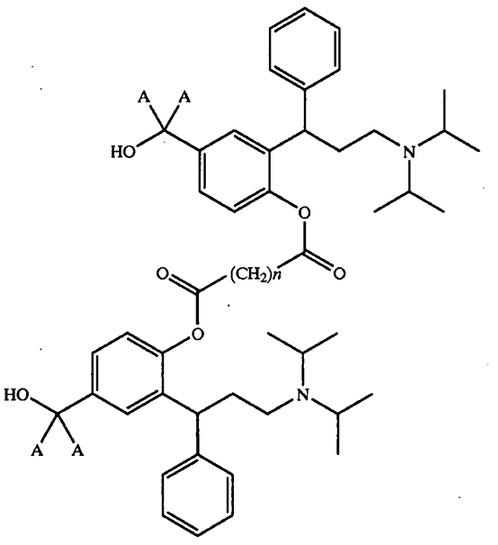
Preferably, the acylating agent is selected from



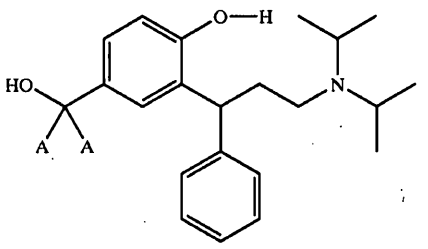
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is a defined above.

A process for the production of phenolic monoesters represented by the general formula I'

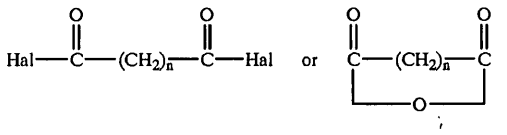
Formula II'



as defined above, which comprises treatment of two equivalents of a compound of the formula

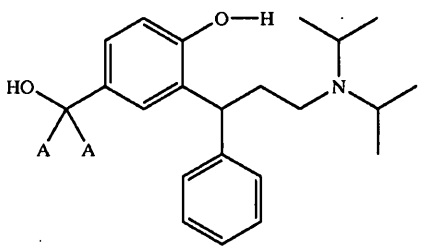


with an acylating agent selected from



wherein Hal represents a halogen atom, preferably a chlorine atom.

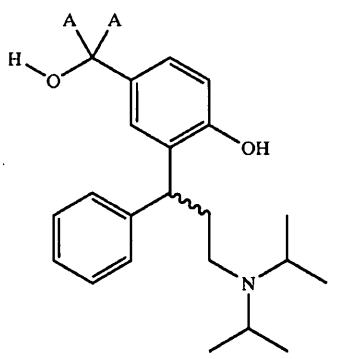
Hence, in these processes, an Intermediate B having the formula



is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n is 0–12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

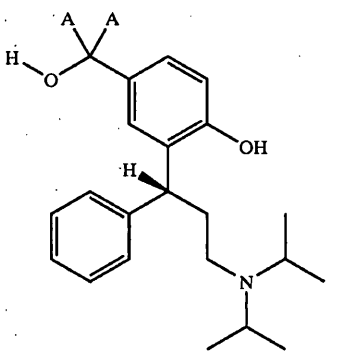
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:

Intermediate RS

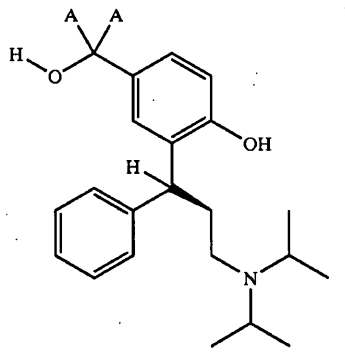


-continued

Intermediate R-(+)



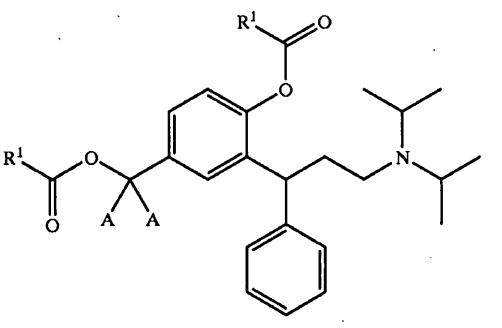
Intermediate S-(-)



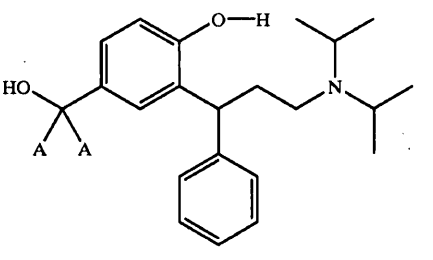
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III

Formula III

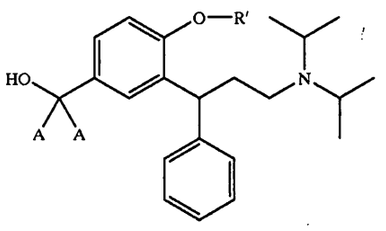


as defined above can be prepared by a process which comprises treatment of a compound of the formula



with at least two equivalents of the acylating agent R^1—C(=O)—LG as defined above.

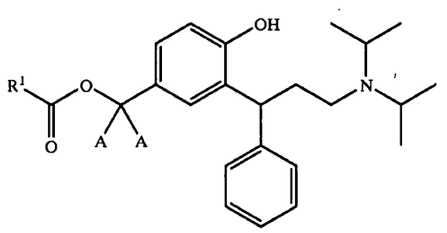
Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



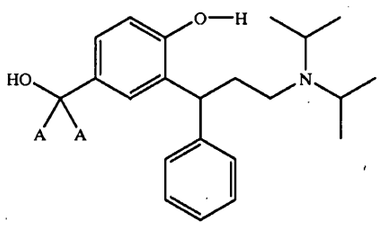
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V

Formula V



wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

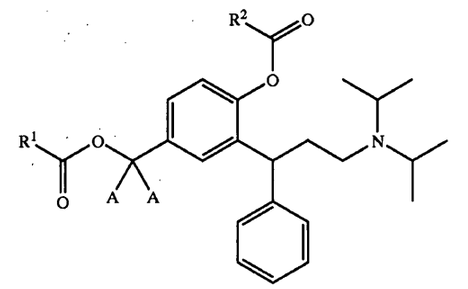


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with para acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can, be removed by known methods (T. W. Greene, P. G. M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room temperature and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

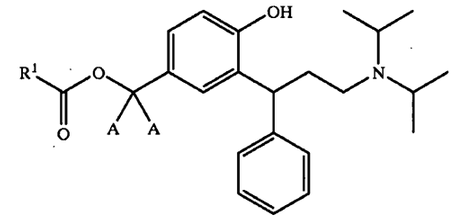
The mixed diesters represented by the general formula IV

Formula IV



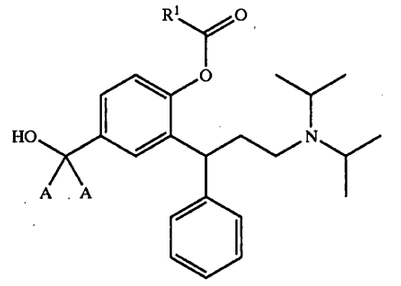
wherein R^1 and R^2 are as defined above can be precared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V

Formula V



wherein R^1 is as defined above or of a phenolic monoester benzylic represented by the general formula II

Formula II

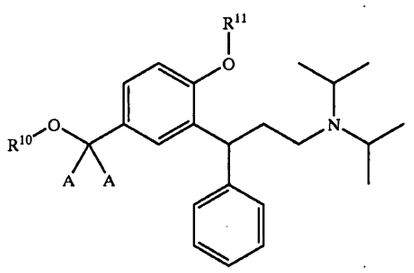


as defined hereinbefore.

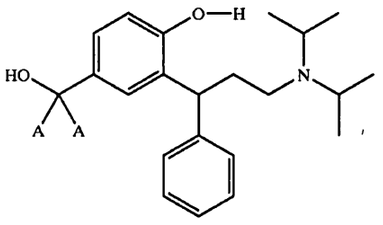
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI

Formula VI



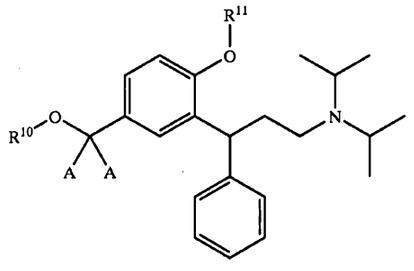
as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



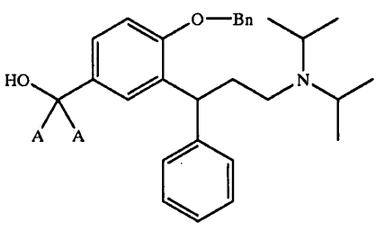
with an alcohol R^{10}—OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

Formula VI



wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

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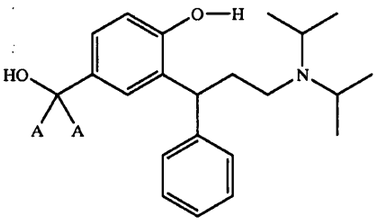
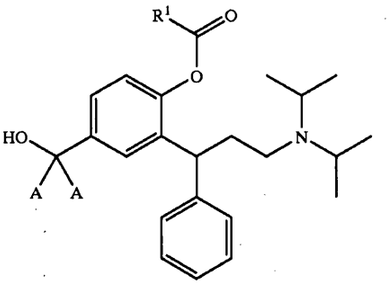


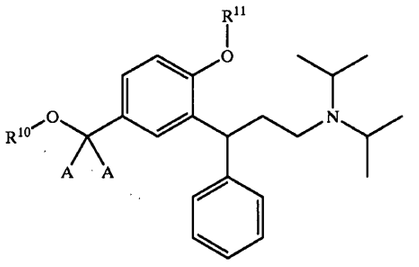
and

Formula II



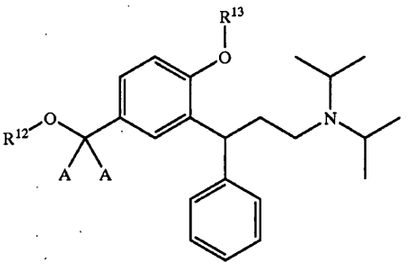
or

Formula VI

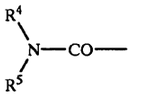


wherein R^{10} is hydrogen and R^{11} is as defined above or

Formula VII



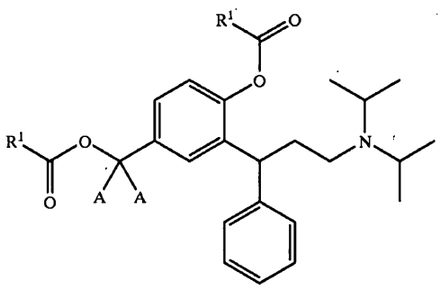
wherein R^{12} is hydrogen and R^{13} represents a C_1–C_6 alkoxycarbonyl group or



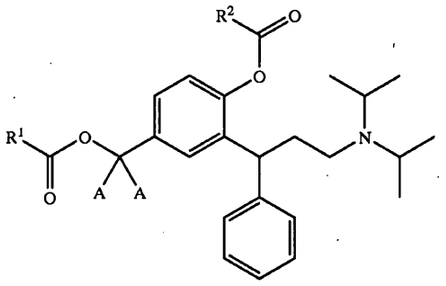
wherein R^4 and R^5 are as defined above

or of benzylic acylates selected from

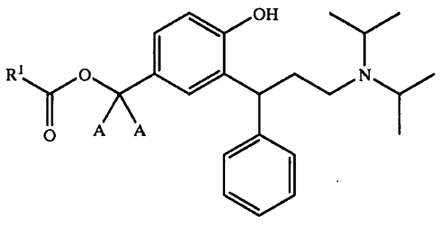
Formula III



Formula IV

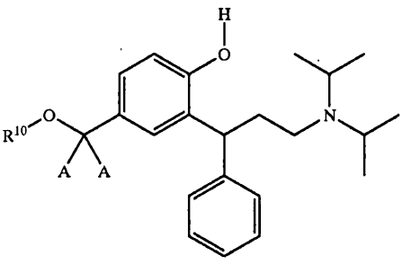


Formula V



wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula



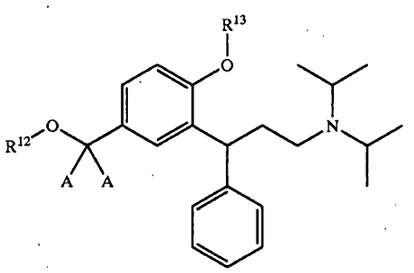
wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

In summary, regioselective modification of the benzylic hydroxy groups is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J. M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P. M. Deya; J. Org. Chem. 53: 4263–4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. 30: 1939–1942 [1989]).

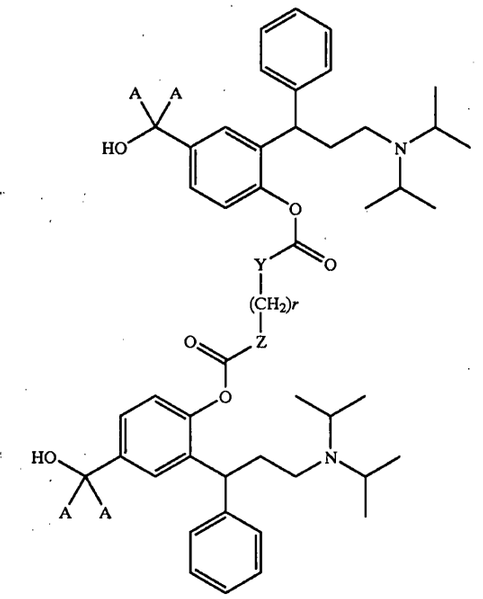
Likewise the phenolic hydroxy groups are readily transformed into phenyl ethers (R^{11}=alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis 1981, 1–28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta 76: 2465–2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. 26: 4307–4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

Formula VII

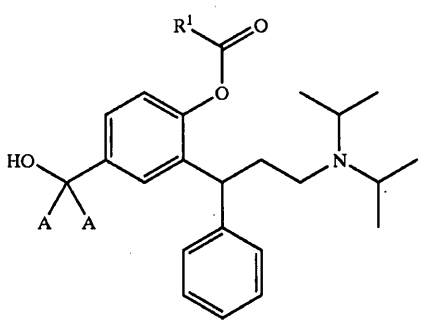


Formula VIII

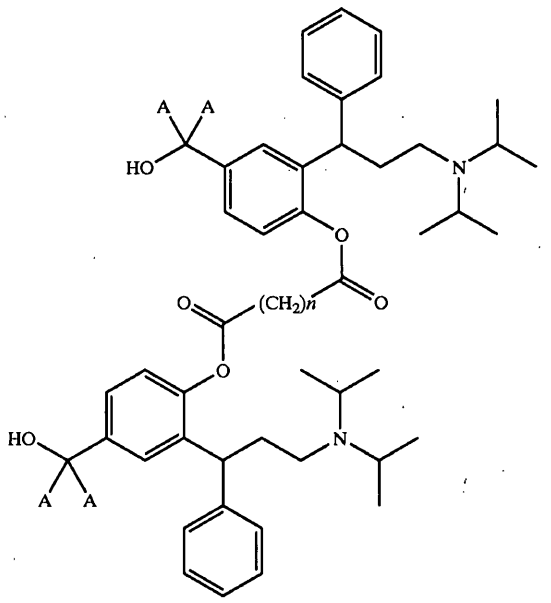


as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of

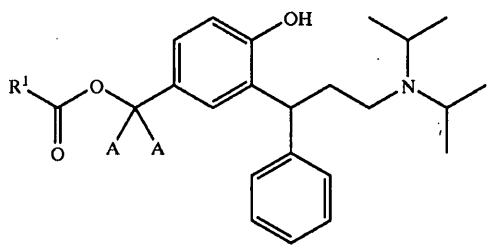
Formula II



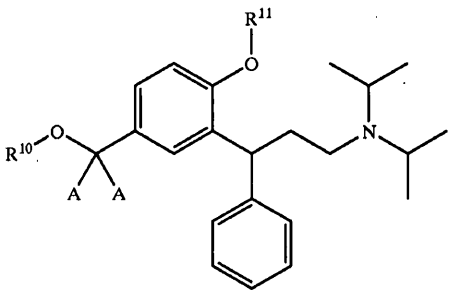
Formula II'



Formula V



Vormula VI



wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from −10° C. to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents —C(=O)—Y—R^3, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphae, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

All compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^1H NMR data (200 MHz, ppm) refer to internal tetramethylsilane). Thin-layer chromatography (tlc, R_f val-

ues reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.

Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).

Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.

Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.

IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.

Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives. Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic Acid 4-Bromophenyl Ester

An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid 3-phenylacrylic acid 4-bromophenyl ester (121.0 g, 99.8% yield), m.p. 113.3° C., tlc: (1) 0.83. NMR ($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with ethylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline (±)-6-bromo-4-phenylchroman-2-one, m.p. 117.8° C., tlc: (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid Methyl Ester

A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2x300 ml) and the extract was washed with water (2x200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46, 126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

A solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50° C. with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4° C. was filtered off and dried in vacuo to yield 0.27 g (71.4%) of (±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid, colourless crystals, m.p. 124.9° C.; tlc: (1) 0.15 starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, M^+), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C, 64.25%, H, 4.66%, Br, 19.43%, O, 11.67%; found: C, 63.72%, H, 4.70%, Br, 19.75%, O, 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4° C. resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly with water and dried to yield (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in 82% yield.

a) Resolution of 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

R-(−)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

Warm solutions of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0° C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g or the ephedrinium salt of the title compound (m.p. 153° C., e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give R-(−)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 7S,2R-(+)-ephedrinium salt in 75% yield, colourless crystalls, m.p. 158.6° C., e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

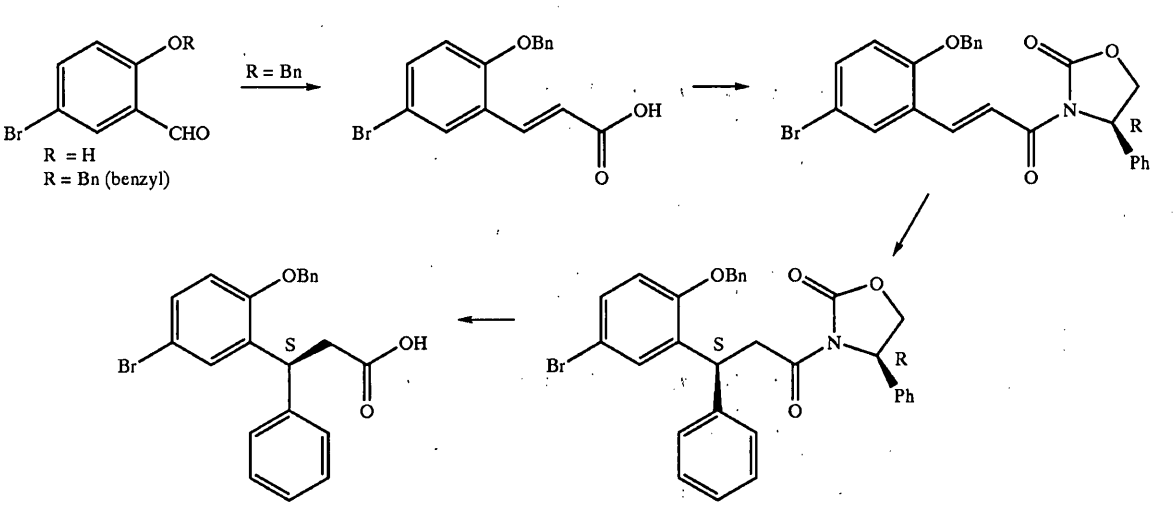
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give R-(−)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6° C. (from ethyl acetate/n-heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ =−21.1 (c=1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemtic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18° C.) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 liter) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+)enantiomeric acid was converted into the 1R,2S-(−)-ephedrine salt as described above for the R-(−) acid. Two recrystallizations from boiling ethanol provided colourless crystals of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(−)-ephedrinium salt in 83% yield, m.p. 158.7° C., e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(−) acid, tlc: (7) 0.20, e.e. (NMR) >99%, mp 105.5° C.; $[\alpha]_D^{20}$ =+22.6 (c=1.0, ethanol); NMR: identical with the racemic acid.

b) Enantioselective Synthesis of R-(−)- and S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromo-benzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic Acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90° C. for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at −30° C. to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to −50° C. and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (−30° C.) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to −40° C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0° C. and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+)enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using

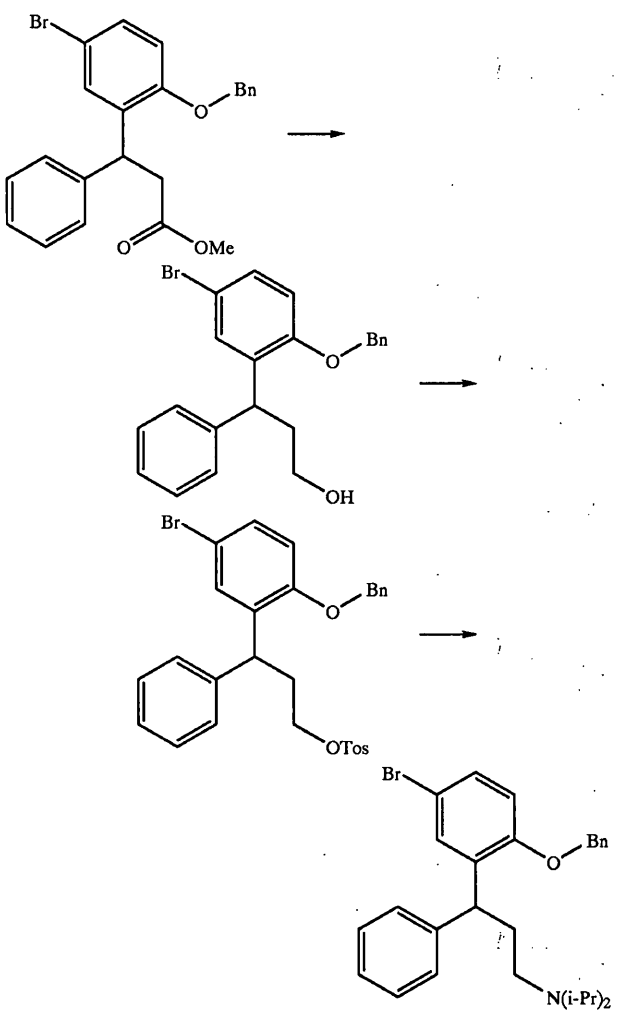
"nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(−)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ =+21.6 (c=0.5, MeOH).

R-(−)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic Acid

Conjugate organocuprate addition of phenylmagnesium-bromide to 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one as described above for the S-(+)enantiomer gave crystalline R-(−)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystallizations, $[\alpha]_D^{22}$ =−21.7 (c=0.5, MeOH).

c) Synthesis of the R- and S-Enantiomers of Intermediate B

(i) Phenylpropanol Route



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminium hydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8° C., tlc: (1) 0.47, (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

The same product was obtained after reduction of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid with lithium aluminium hydride in tetrahydrofuran (30 min, 25° C.), 31% yield.

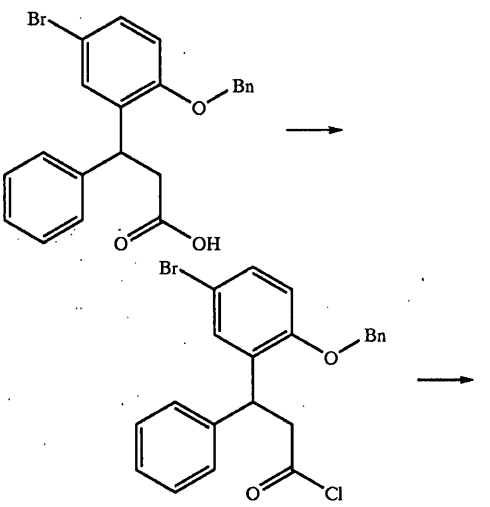
(±)-Toluene-4-sulphonic Acid 3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl Ester

A cooled (5° C.) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give (±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12–13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide (±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a brown and viscous syrup (94.5 g, 77.9% yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



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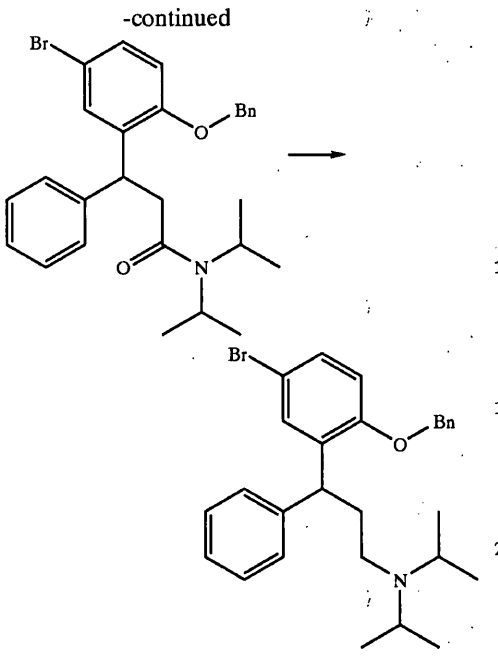


S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl Chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3° C.) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temperature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 69.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

The amide was prepared from duisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at −30° C. From this solution colourless crystals were obtained, m.p. 101.8° C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10–12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc: (4) 0.86. The NMR spectrum corresponds to the product, obtained from the tosylate precursor (see above).

S-(+)-13-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ =+18.5 (c=10.0, ethanol), e.e. of a representative batch 99.4%.

R-(−)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(−)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(−)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ =−17.3 (c=10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic Acid Hydrochloride

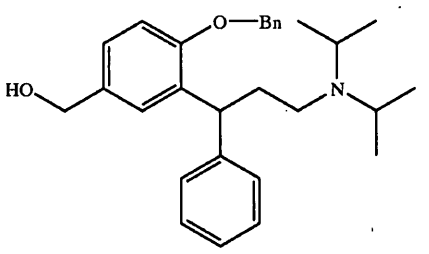
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to −60° C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to pH 0.95, a white solid was recovered by filtration to provide (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride (14.7 g, 64.3% yield), m.p. 140° C. (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n=1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6 h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2 h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4° C., tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.

Intermediate A



(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n=2)

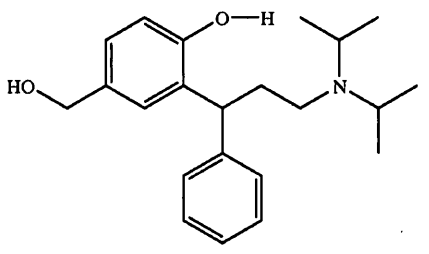
Repetition of the above described reduction of the methylester of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centered at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Intermediate B (n=1)

A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, (±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, m.p. 50° C., tlc: (2) 0.15. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38. Hydrochloride: colourless crystalls, m.p. 187–190° C. (with decomposition).

Intermediate B



S-(−)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Hydrogenolysis of S-(−)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. >50° C., $[\alpha]_D^{22}$ =−19.8 (c=1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52. S-(+)hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4° C. (dec.); $[\alpha]_D^{22}$ =+6.6 (c=0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Hydrogenolysis of R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol (prepared from R-(−)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield, colourless solid; m.p. ≧50° C., $[\alpha]_D^{22}$ =+21.3 (c=1.0, ethanol). R-(−) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8° C. (dec.); $[\alpha]_D^{22}$ =−7.2 (c=0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79. R-(+)-mandelate: m.p. 139.7° C., $[\alpha]_D^{21}$ =+38.3 (c=1.0, ethanol).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

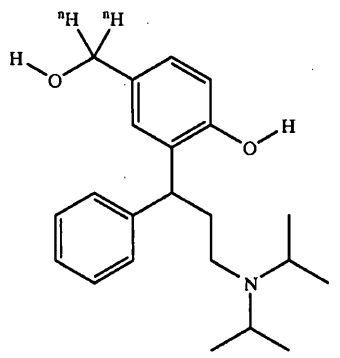
Intermediate d_2-B (n=2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1° C.; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centered at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1–0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2×5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46–49° C. Tlc: (4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53,

155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).

Intermediate d_2-B

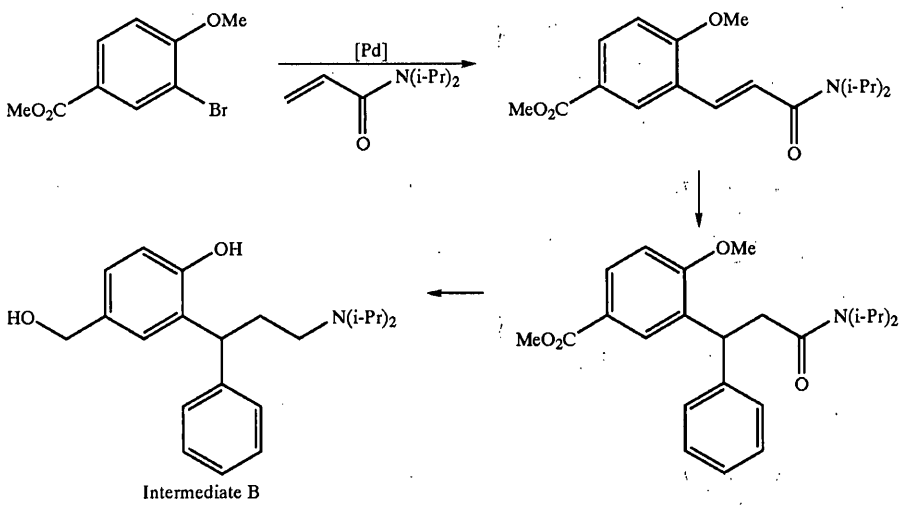


n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0–5° C.) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3×100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic Acid Methyl Ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol %), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130° C. until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139–140° C., tlc: (1) R_f 0.40. NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07. MS (EI, DI, 105° C.): 319 (M^+, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxybenzoic Acid Methyl Ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclohexane/diethyl ether) to a cooled (0° C.) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to −78° C. and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at −78° C., warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide as a viscous slightly yellow syrup (1.8 g, 44% yield). NMR

(CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105° C.): 397 (M^+, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5° C. and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room temperature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5° C. by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48–51° C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186–189° C. (dec.).

Hydrogenolytic Deoxygenation of S-(−)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of S-(−)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ =+19.8 (c=1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(−)-tartaric acid (300 mg) and storage of the clear solution at −25° C. gave colourless crystals (310 mg) of S-(−)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(−)hydrogentartrate in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ =−26.7 (c=1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ =−26.3 (c=1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:

- (±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
- R-(−)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
- S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
- (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
- S-(−)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
- R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Example

a) Phenolic Monoesters

aa) General Procedure

Eaters of Carboxylic Acids

A stirred solution of (±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid monochloride for compounds of formula II, 2.50 mmol for compounds of formula II') in 60 ml of dichloromethane was cooled to 0° C. and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5–10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2–4 hrs.) to remove traces of residual solvents.

The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in puritees between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5° C. in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2–8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt Formation (Example hydrochloride)

A cooled (0° C.) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100° C. (with decomposition).

The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%).

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%).

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16, 43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-CI (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-CI (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%).

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36.

R-(+)-Isobutyric Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39. Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ =+5.5 (c=1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%).

(±)-2-Acetamidoacetic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)

NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82.

(±)-Cyclopentanecarboxylic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.66 (4), starting material Intermediate B 3 (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.67 (4), starting material Intermediate B 3 (0.50) colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.

(±)-Benzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity >95%); gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

R-(+)-Benzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

tlc R_f 0.30 (4); colourless syrup; Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ =+14.9 (c=1.0, chloroform); NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.8, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 34.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07. LC-MS: 459 (M^+, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 (M^+, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 (M^+, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 (M^+, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 (M^+, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 (M^+, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic Acid 2-(3-Diisopropylamino-7-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27,

131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 (M^+, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 (M^+, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6° C.; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 (M^+, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 (M^+, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester/(±)-2-Acetamidoacetic Acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(Acetylamino)acetate)

NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic Acid bis-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23, 64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54.

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01.

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05.

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 121.80, 136.99, 138.94, 143.82, 147.65, 168.72.

b) Identical Diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine and acyl chloride (R^1—COCl) were used. The physical properties were similar to the bases and salts described above.

Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* 37: 45–58 [1954]).

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$): 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42.

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc: R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%).

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76, 148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%).

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%).

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%).

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60.

(±)-Benzoic Acid 4-Benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl Ester

Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ −+24.2 (c=1.0, chloroform). NMR ($DMSO\text{-}d_6$): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) Mixed Diesters

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95.

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78.

(±)-Benzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl Ester

Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+)enantiomer, see below.

R-(+)-Benzoic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl Ester

tlc: R_f 0.70 (4); Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ =+27.1 (c=1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53, 21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl Ester

colourless oil; Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ =+14.6 (c=1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40.

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60.

d) Benzylic Monoesters

A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 9) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2–24 hrs complete disappearence of the starting material (R_f=0.45 (3)). The mixture was filtered and then evaporated under high vacuum (<40° C.) to give the carboxylic acid (R^1—CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32.

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2); NMR ($CDCl_3$): 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44.

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22.

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05.

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR (CD)CO_3): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48.

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39.

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60.

e) Ethers and Silyl Ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol)/ and alcohol R^{10}—OH (50–150 ml) was stirred at room temperature until no starting material was detectable (2–24 hrs). After evaporation to dryness (<35° C.) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100–200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11}=H) as colourless to light yellow oils.

Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

Molar equivalents of bases of formula VI (R^{11}=H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%); hydrochloride: amorphous hygroscopic colourless solid; m.p. 161° C.; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol, tlc: R_f 0.72 (4); GC-MS/P-CI

(ammonia, triethylsilyl derivative): 444.8 (100%), 398.4 (6%); hydrochloride: colourless non-hygroscopic crystals, m.p. 158–161° C., NMR (CD_3OD) 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopronoxymethylphenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65. Hydrochloride: colourless crystals, m.p. 140.400, tlc (4) 0.61. LC-MS: 383 (6%, $[M-HCl]^+$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28, 39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36.

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128.35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95.

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28.

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98.

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06.

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09.

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28.

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3).

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): –4.92, –5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20.

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%).

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$): –4.77, –4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95.

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7 (78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%).

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94.

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$): 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%).

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%).

f) Carbamates and Carbonates

Mono N-substituted Carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11}=H) or monoester of formula II in dichloromethane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanaze (2.2 mmol). After washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0° C.) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65° C. over 18 hrs.

Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation

to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64° C. (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52.

(±)-N,N-Dimethylcarbamic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97.

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00.

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino)acetic Acid Ethyl Ester Hydrochloride

Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72, 130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71.

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3); NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74.

(±)-N,N-Dimethylcarbamic Acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl Ester

NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

(±)-N,N-Diethylcarbamic Acid 3-(3-Diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl Ester

NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

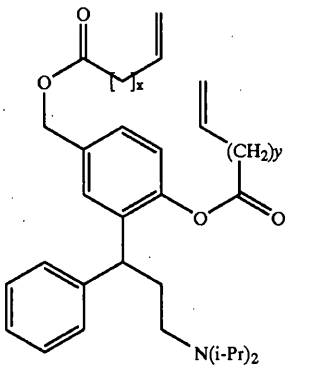
(±)-{4-C2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]-butyl}-carbamic Acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl Ester

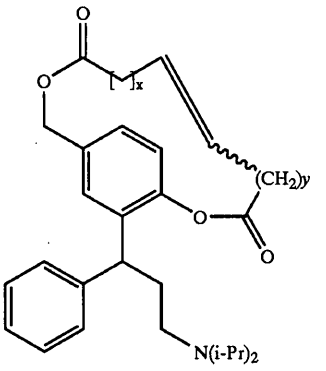
(formula VII', X=Y=NH, n=4) tlc: R_f 0.60 (6); dihydrochloride m.p. 142.5–145.6° C.

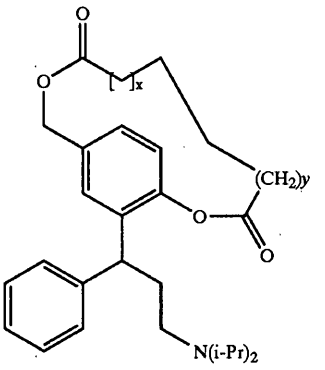
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4).

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4).

g) Intramolecular Cyclic Diesters Via Ring Closing Metathesis (RCM)







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl Ester (x=y=2)

A cooled (4° C.) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane 30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave (±)-pent-4-enoic acid 2-(3-diisopropyl amino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular Cyclic Diesters of 1,ω-Dioic Acids and Intermediate B

Example:

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of (±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed an vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the presence of palladium-on carbon catalyst to afford the intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (>1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml), was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000–4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as described to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000–8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn or 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5° C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30–1.60 ppm

CH resonances of the poly-lactyl chain: 5.10–5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8–5.0 ppm and 5.5–5.7 ppm.

Polymer bound Intermediate B: 1.06–1.11 (CH_3), 2.20–2.30 ($CH_2\underline{CH_2}$), 2.40–2.80 ($N\underline{CH_2}$), 3.30–3.50 ($N\underline{CH}$), 4.45–4.55 ($\underline{CH}CH_2$), 4.70–4.80 ($\underline{CH_2}$—OCO-lactyl), 6.70–7.30 (aryl $\underline{CH}$).

h) Inorganic Ester

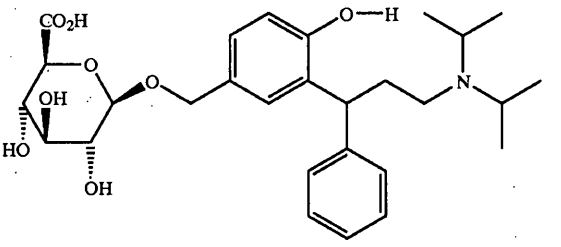
Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl Ester Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0° C. a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed Immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63–65° C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to −25° C. under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrae was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-

%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions cave (±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.51, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22° C.). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of (±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol, sodium salt, amorphous colourless solid, m.p. ≅110–124° C. (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of Different Compounds of the Invention With Human Liver S 9-Fraction

a) Incubation of Unlabelled Substrates

A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, Mass., USA.

In a routine assay, 25 μL of pooled human liver S 9 (20 mg protein/mL, H961, Gentest, Woburn, Mass., USA) was incubated for 2 hrs at 37° C. with 40 μM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchioric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

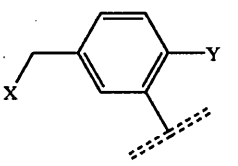
The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in FIG. 1.

They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

The prodrugs introduced in the assay show the following chemical structure:



chemical structure X-/-Y		
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate
iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
Propo-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of Labelled Substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0° C. in a concentration of 40 μM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor Binding Study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes a 25° C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(−)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholineruic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs, solution (pH 7.4, 32° C.) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(−)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological Membranes

Different compounds of the invention were tested or their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32° C. according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99–101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV detection 220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds oft the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24$ hrs]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

Disubstitution of the hydroxy group of HO—/—OH leads to a ≧20-fold increase in skin permeation in relation to the parent HO—/—OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

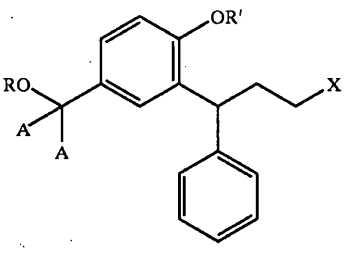
Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S 9 preparation.

Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

What is claimed is:

1. A 3,3-Diphenylpropylamine of the general formula I:

Formula I



wherein R and R' are independently

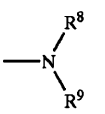
a) hydrogen; or

b) formyl, C_1–C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstitited arylcarbonyl;

with the proviso that R' is not hydrogen, methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia

Formula Ia

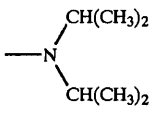


wherein R^8 and R^9 represent C_1–C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

A represents hydrogen (^1H) or deuterium (^2H), and

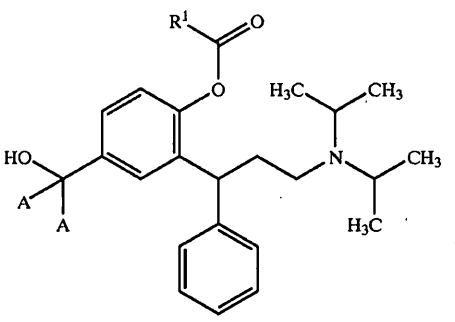
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. The 3,3-Diphenylpropylamine as claimed in claim 1, wherein X is

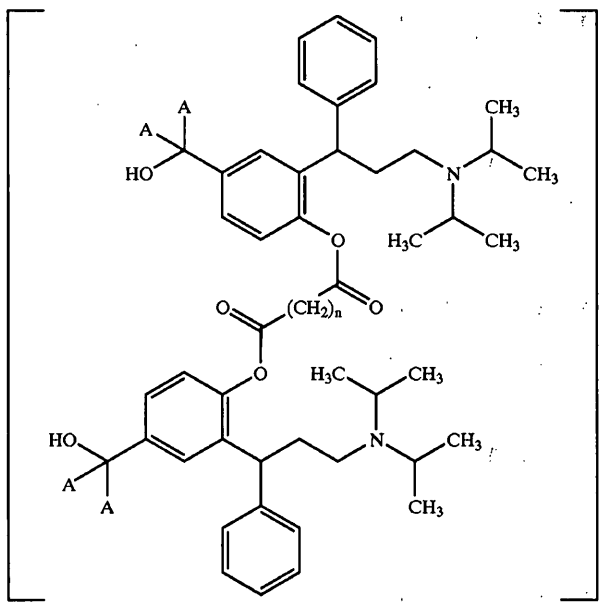


3. The 3,3-Diphenylpropylamine as claimed in claim 2 selected from phenolic monoesters represented by the general formula II

Formula II



Formula II'



wherein R^1 represents hydrogen, C_1–C_6 alkyl or phenyl.

4. The 3,3-Diphenylpropylamine as claimed in claim 2 selected from:

(±)-formic acid 2-(3diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2methylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

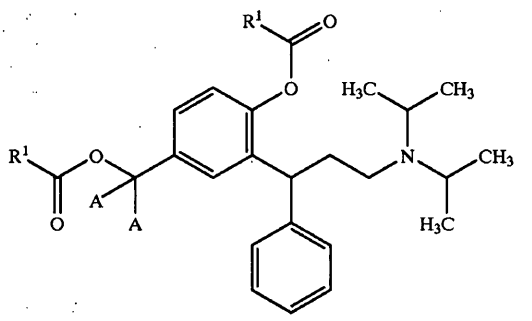
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and

(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

5. The 3,3-Diphenylpropylamine as claimed in claim 2 represented by the general formula III

Formula III



wherein R^1 is hydrogen, C_1–C_6 alkyl or phenyl.

6. The 3,3-Diphenylpropylamine as claimed in claim 5 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,

(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester,

(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

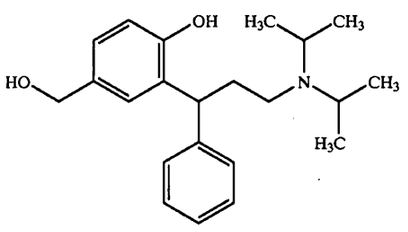
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,

cyclic oct-4-ene-1,8-dioate of Intermediate B,

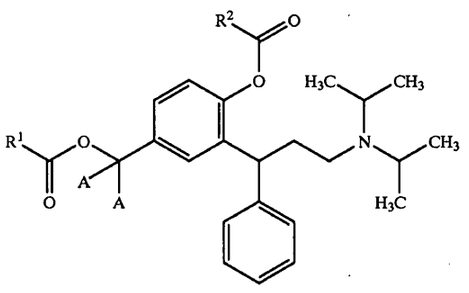
cyclic octane-1,8-dioate of Intermediate B, and

poly-co-DL-lactides of Intermediate B, said Intermediate B having the formula



7. The 3,3-Diphenylpropylamine as claimed in claim **2** selected from mixed diesters represented by the general formula IV

Formula IV



wherein R^1 is hydrogen, C_1–C_6 alkyl or phenyl, and R^2 represents hydrogen, C_1–C_6 alkyl or phenyl with the proviso that R^1 and R^2 are not identical.

8. The 3,3-Diphenylpropylamine as claimed in claim **7** selected from:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester, R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,

(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

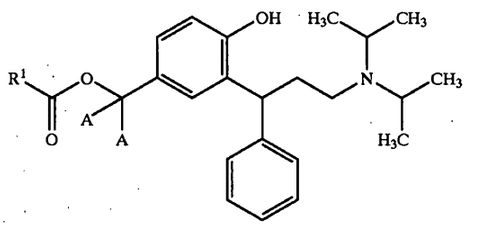
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, and

(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. The 3,3-Diphenylpropylamine as claimed in claim **2** selected from benzylic monoesters represented by the general formula V

Formula V



wherein R^1 is hydrogen, C_1–C_6 alkyl or phenyl.

10. The 3,3-Diphenylpropylamine as claimed in claim **9** selected from:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

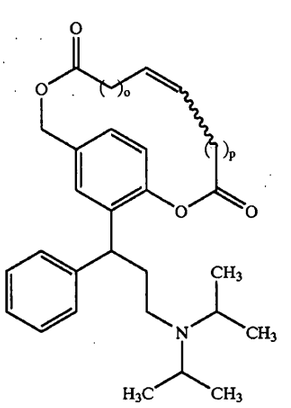
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, and

(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. A 3,3-Diphenylpropylamine selected from

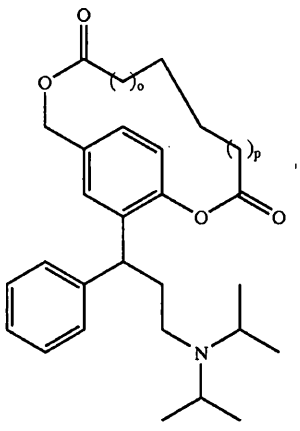
(i) compounds of the formulae IX and IX'

Formula IX



-continued

Formula IX'

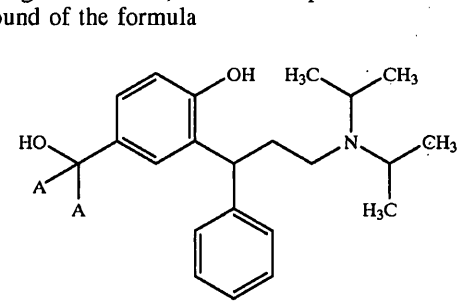


wherein o and p are the same or different and range from 0 to 6,

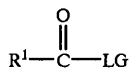
(ii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethylphenol and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

12. A process for the production of phenolic monoesters according to claim **3**, which comprises treatment of a compound of the formula

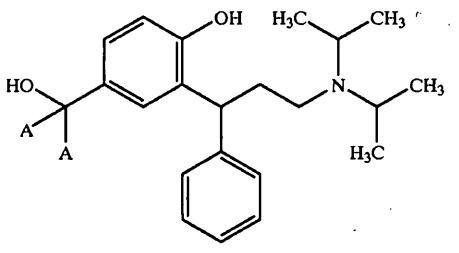


with an equivalent of an acylating agent of formula

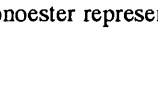


wherein LG represents a leaving group selected from halide, carboxylate and imidazolide in an inert solvent in the presence of a condensing agent.

13. A process for the production of identical diesters according to claim **5**, which comprises treatment of a compound of the formula

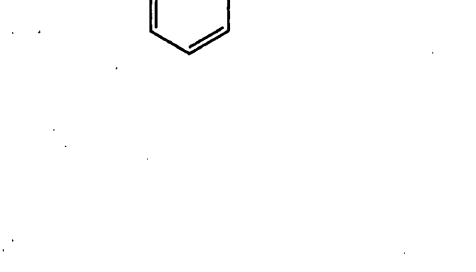


with at least two equivalents of the acylating agent of formula



wherein LG represents a leaving group selected from halide, carboxylate and imidazolide in an inert solvent in the presence of a condensing agent.

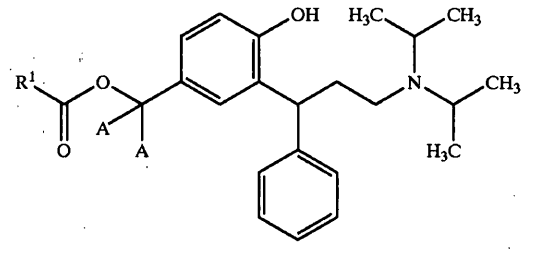
14. A process for the preparation of benzylic monoesters according to claim **9**, which comprises treatment of a compound of the formula



at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

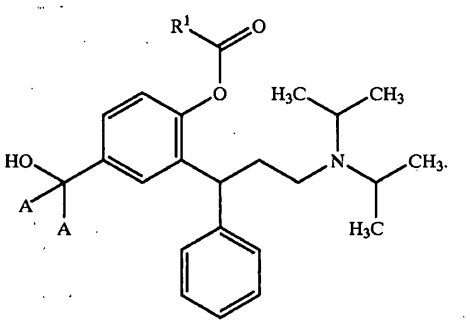
15. A process for the preparation of mixed diesters according to claim **7**, which comprises acylation of a benzylic monoester represented by the general formula V

Formula V



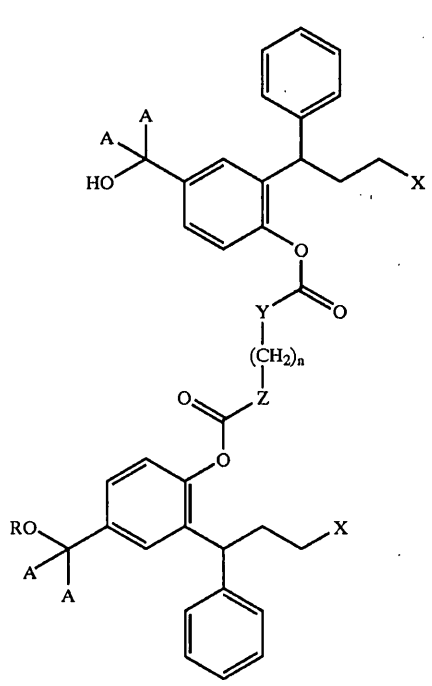
or of a phenolic monoester represented by the formula II

Formula II



16. A 3,3-Diphenylpropylamine of the general formula VII':

Formula VII'



wherein R is

a) hydrogen; or

b) formyl, C_1–C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl;

X represents a tertiary amino group of formula Ia

Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

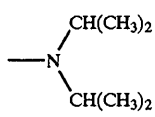
Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12, and

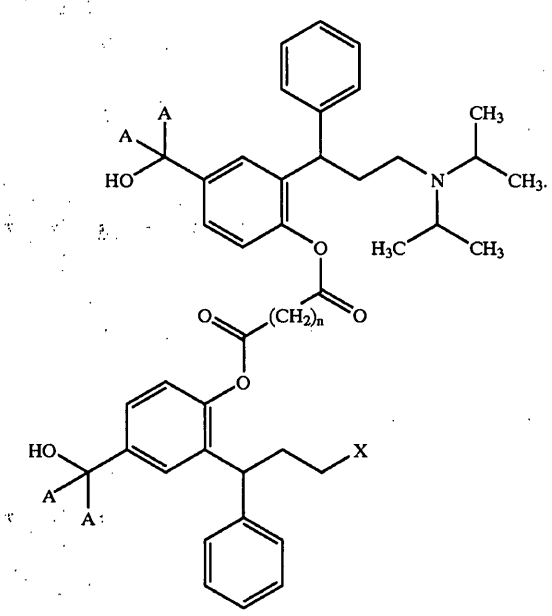
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

17. The 3,3-Diphenylpropylamines as claimed in claim **16**, wherein X is

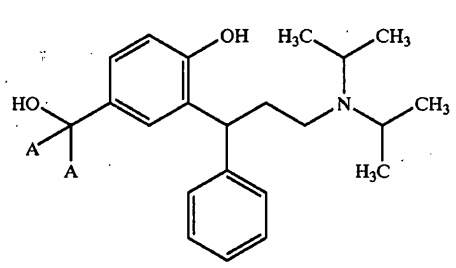


18. The 3,3-Diphenylpropylamine as claimed in claim **17**, selected from phenolic monoesters represented by the general formula II'

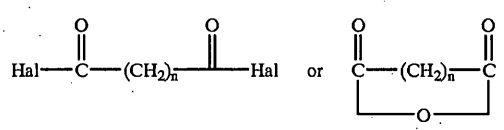
Formula II'



19. A process for the production of phenolic monoesters according to claim **18**, which comprises treatment of two equivalents of a compound of the formula



with an acylating agent of formula



wherein Hal represents a halogen atom.

20. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims **1–10**, **11** and **16–18** and a pharmaceutically acceptable carrier.

21. A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims **1–10**, **11** and **16–18**.

22. A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering an amount of a composition according to claim **20** effective to diminish or eliminate symptoms of the disease.

23. The method according to claim **22** wherein the disease is urinary incontinence.

24. The method according to claim **23** wherein the mammal is a human.

25. A 3,3-Diphenylpropylamine selected from:

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester,

(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester, and

(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester.

26. The 3,3-Diphenylpropylamine of claim **2**, wherein the 3,3-Diphenylpropylamine is R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a pharmaceutically acceptable salt thereof.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,464 B1
DATED : March 30, 2004
INVENTOR(S) : Claus Meese and Bengt Sparf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 9, delete "hydrocaryl" and insert therefor -- hydrocarbyl --.
Line 43, delete "$R^{8 \text{ and } R9}$" and insert therefore -- R^8 and R^9 --.

Column 8,
Line 21, after "formula" add -- III --.

Column 9,
Line 18, delete "R" and insert therefor -- R^2 --.

Column 10,
Line 49, delete "2-trimehylsilanyl" and insert therefor -- 2-trimethylsilanyl --.

Column 11,
Line 9, delete "3-d4isopropyl" and insert therefor -- 3-diisopropyl --.

Column 13,
Line 47, delete "he" and insert therefor -- the --.

Column 14,
Line 38, after "formula" delete "I'" and insert therefor -- II' --.

Column 17,
Line 64, delete "can, be" and insert therefor -- can be --.

Column 18,
Line 23, delete "precared" and insert therefor -- prepared --.

Column 24,
Line 31, delete "phosphae" and insert therefor -- phosphate --.

Column 26,
Line 49, delete "7S,2R" and insert therefor -- 1S,2R --.

Column 31,
Line 53, delete "69.61" and insert therefore -- 169.61 --.
Line 56, delete "duisopropylamine" and insert therefor -- diisopropylamine --.

Column 32,
Line 11, delete "13-(2" insert -- [3-(2 --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,464 B1
DATED : March 30, 2004
INVENTOR(S) : Claus Meese and Bengt Sparf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 34,
Line 21, delete "R-(+)" and insert therefor -- S-(+) --.

Column 38,
Line 4, delete "Eaters" and insert therefor -- Esters --.

Column 39,
Lines 47 and 55, delete "Intermediate B.3 (0.50)" and insert therefor -- Intermediate B (0.50) --.

Column 40,
Line 6, delete "127.8" and insert therefor -- 127.58 --.
Line 8, delete "34.27" and insert therefor -- 134.27 --.
Line 62, delete "Diisopropylamino-7-phenyl" and insert therefor -- Diisopropylamino-l-phenyl --.

Column 41,
Line 61, delete "121.80" and insert therefor -- 131.80 --.

Column 45,
Line 11, delete "isopronoxymethylphenol" and insert therefor -- isopropoxymethylphenol --.
Line 14, delete "140.400" and insert therefor -- 140.4 °C --.
Line 44, delete "diisocyanaze" and insert therefor -- diisocyanate --.

Column 47,
Line 30, delete "amino)acetic" and insert therefor -- amino]acetic --.
Line 53, delete "4-C2-" and insert therefor -- 4-[2- --.

Column 51,
Line 4, delete "cave" and insert therefor -- gave --.
Line 53, delete "perchioric" and insert therefor -- perchloric --.

Column 52,
Line 21, delete "Propo-/" and insert therefor -- PropO-/ --
Line 54, delete "receptors" and insert therefor -- receptors. --

Column 53,
Line 56, delete "tested or" and insert therefor -- tested for --.
Line 66, delete "oft he" and insert therefor -- of the --.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,713,464 B1
DATED : March 30, 2004
INVENTOR(S) : Claus Meese and Bengt Sparf

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

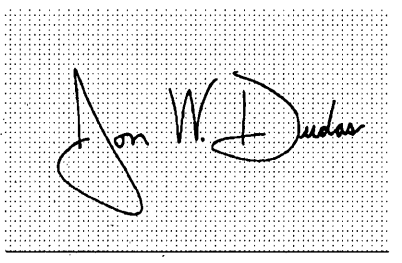
Column 55,
Lines 25-48, delete formula II.
Line 53, delete "3diisopropyl" and insert therefor -- 3-diisopropyl --.
Line 66, delete "2,2-methylpropionic" and insert therefor
-- 2,2-dimethylpropionic --.

Column 56,
Line 13, delete "propyl)hydroxyl" and insert therefor -- propyl)-4-hydroxy --.

Column 57,
Lines 54-58, insert a line break before the compound "R-(+)- benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester".

Signed and Sealed this

Thirty-first Day of May, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

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Bib Data Sheet

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/700,094	01/02/2001 RULE –	514	1614	MBHB00-1121

APPLICANTS

Claus Meese, Monheim, GERMANY;
Bengt Sparf, Trangsund, SWEDEN;

** CONTINUING DATA **********

THIS APPLICATION IS A 371 OF PCT/EP99/03212 05/11/1999

** FOREIGN APPLICATIONS **********

EUROPEAN PATENT OFFICE (EPO) 98108608.5 05/12/1998

IF REQUIRED, FOREIGN FILING LICENSE GRANTED 01/26/2001

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☒ yes ☐ no	GERMANY	1	1	1

35 USC 119 (a-d) conditions met ☒ yes ☐ no ☐ Met after Allowance

Verified and Acknowledged Examiner's Signature Initials

ADDRESS

20306

TITLE

Novel derivatives of 3,3-diphenylpropylamines

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2160	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other ☐ Credit

patent application serial no.

Department of Commerce
Patent and Trademark Office
fee record

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01 FC:970 860.00 OP
02 FC:966 900.00 OP
03 FC:968 270.00 OP

Express Mail 526 Rec'd PCT/PTO 08NOV2000

FORM PTO-1390 (Modified) (REV 11-98) U.S DEPARTMENT COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: ML 00-1121

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR): 09/700094

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03212	11 May 1999	12 May 1998

TITLE OF INVENTION
Novel Derivatives of 3,3-Diphenylpropylamines

APPLICANT(S) FOR DO/EO/US
Claus Meese
Bengt Sparf

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S C 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   - a ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - b ☐ has been transmitted by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   - a ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - b. ☐ have been transmitted by the International Bureau.
   - c ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S C. 371(c)(3))
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U S C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording A separate cover sheet in compliance with 37 CFR 3 28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

PTO Form 1449 and three (3) cited references
Acknowledgement Postcard

PCTUS1/REV03

529 Rec'd PCT/PTC 08 NOV 2000

U.S. APPLICATION NO. (IF KNOWN, SEE 09/700C	INTERNATIONAL APPLICATION NO. PCT/EP99/03212	ATTORNEY'S DOCKET NUMBER MBHB00-1121

2. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	$970.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	$840.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$690.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$670.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	70 - 20 =	50	x $18.00	$900.00
Independent claims	3 - 3 =	0	x $80.00	$0.00
Multiple Dependent Claims (check if applicable).			☒	$270.00

TOTAL OF ABOVE CALCULATIONS =		$2,030.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1 28) (check if applicable).	☐	$0.00
SUBTOTAL =		$2,030.00
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).	+	$0.00
TOTAL NATIONAL FEE =		$2,030.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).	☐	$0.00
TOTAL FEES ENCLOSED =		$2,030.00
	Amount to be: refunded	$
	charged	$

☒ A check in the amount of **$2,030.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-2490** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Michael S. Greenfield

20306
PATENT TRADEMARK OFFICE

SIGNATURE

Michael S. Greenfield
NAME

37,142
REGISTRATION NUMBER

14-8-00
DATE

Description

Novel derivatives of 3,3-diphenylpropylamines

~~THIS APPLICATION WAS FILED UNDER 35 U.S.C. 371 AND IS THE U.S. NATIONAL STAGE OF PCT/EP99/03212, FILED 11 MAY 1999.~~

The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to

result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage com-

pared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

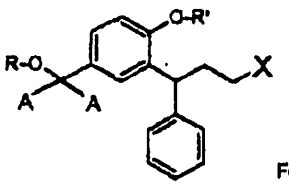
However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

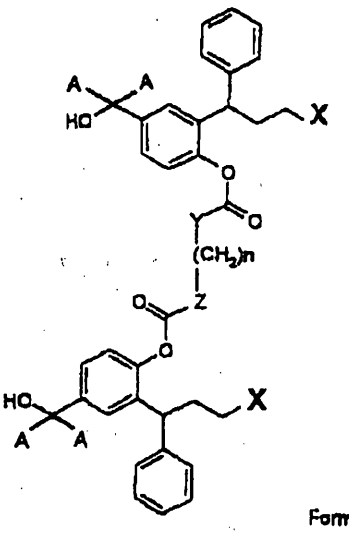
A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds

and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

According to the present invention, novel 3,3-diphenylpropylamines are provided, which are represented by the general formulae I and VII



Formula I



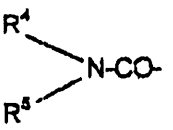
Formula VII

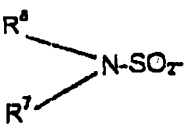
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

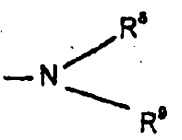
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

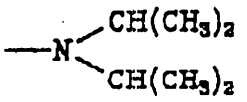
The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

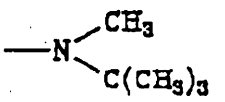
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

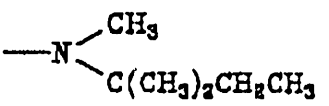
Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-6}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

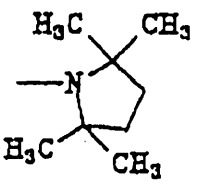
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

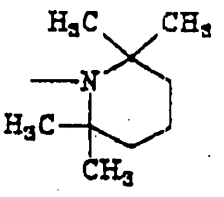
Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

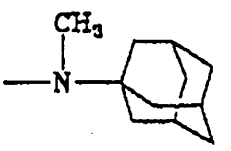
a) 

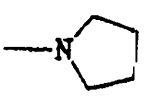
b) 

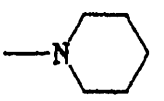
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-), anthryl- ($C_{14}H_9$-), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula $-CO-C_6H_5$ wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. As substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and correponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

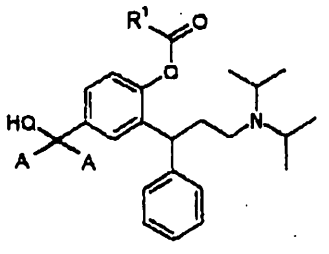
The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

The term "Bn" as used herein denotes a benzyl group.

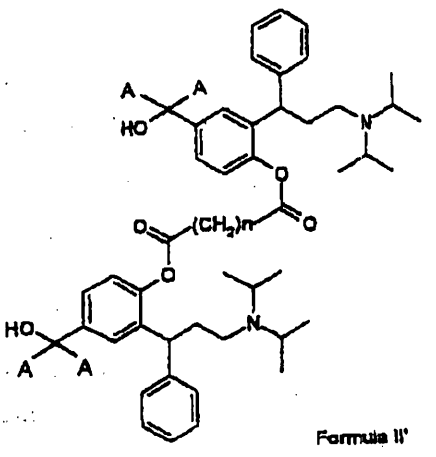
Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

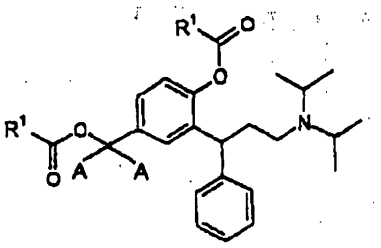
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



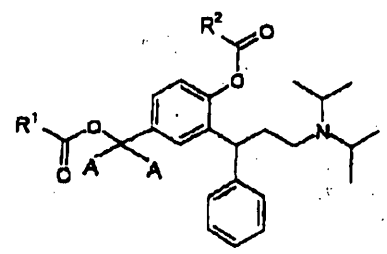
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is as defined above

and

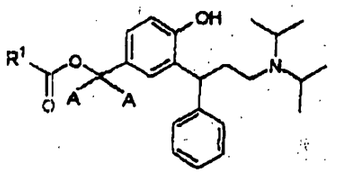
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



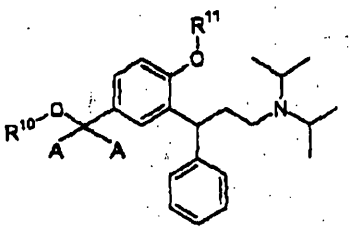
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

Particularly preferred ethers and silyl ethers are listed below:

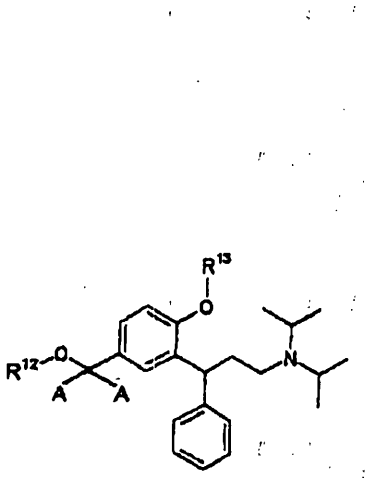
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxy-methyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

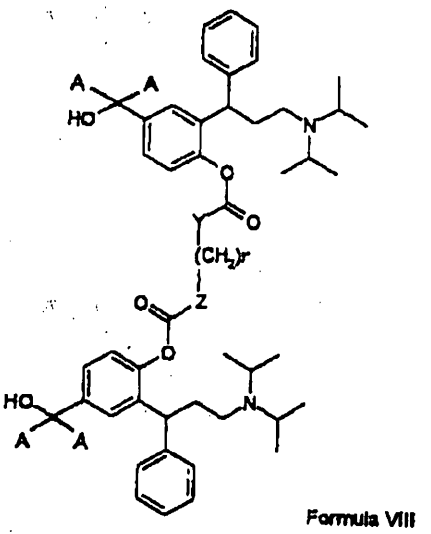
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

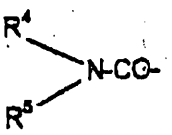


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

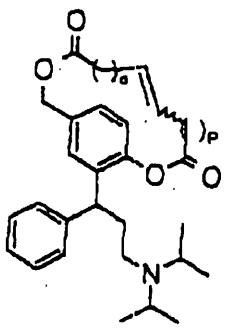
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

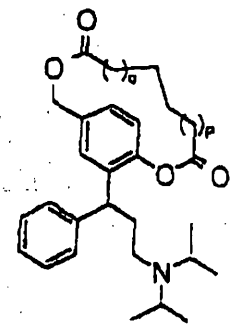
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



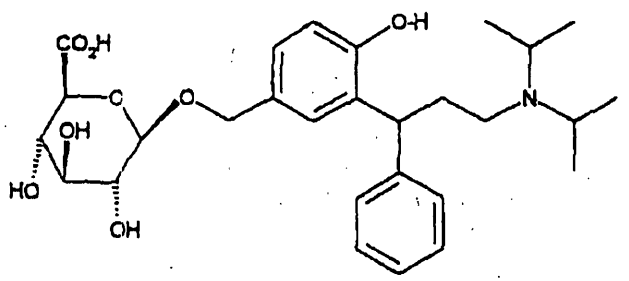
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $+CH_2+$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

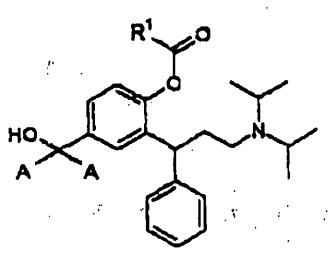


and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

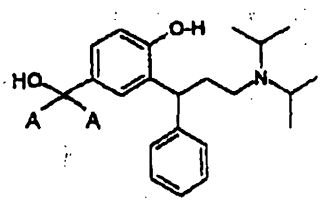
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II

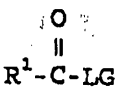


Formula II

as defined above, which comprises treatment of a compound of the formula

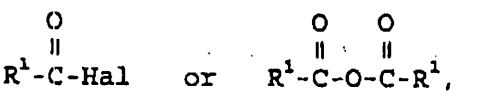


with an equivalent of an acylating agent selected from



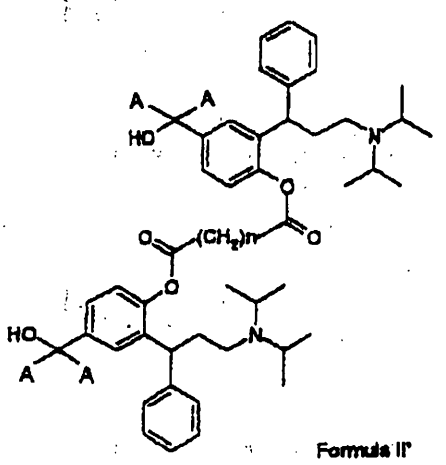
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

Preferably, the acylating agent is selected from



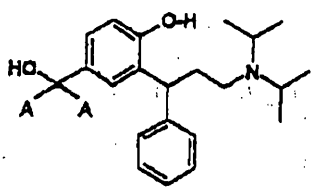
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

A process for the production of phenolic monoesters represented by the general formula II'

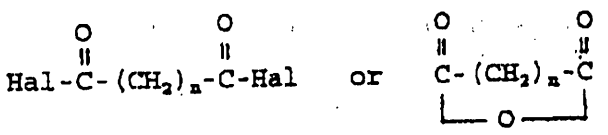


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

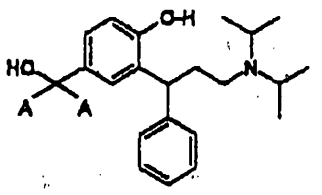


with an acylating agent selected from



wherein Hal represents a halogen atom, preferably a chlorine atom.

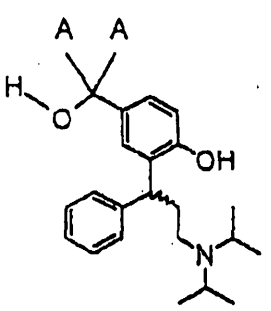
Hence, in these processes, an Intermediate B having the formula



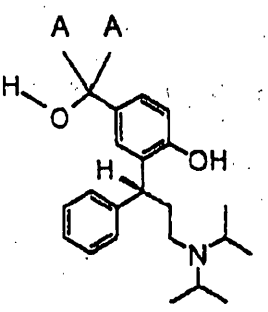
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n

is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

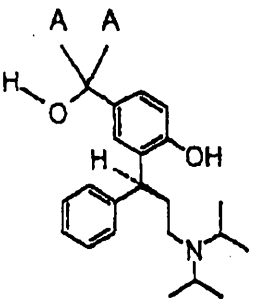
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



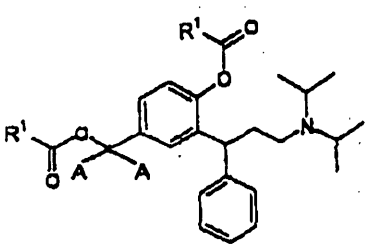
Intermediate R-(+)



Intermediate S-(-)

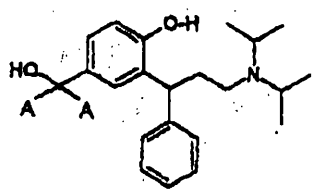
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III



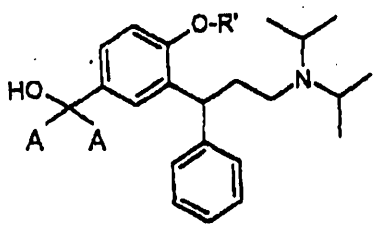
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



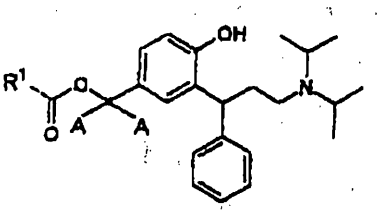
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

Thus, the aforementioned di-acyl compounds are readily accessible if an at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



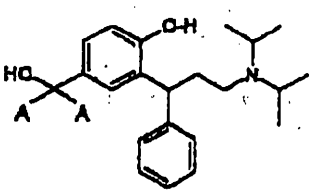
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V



Formula V

wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

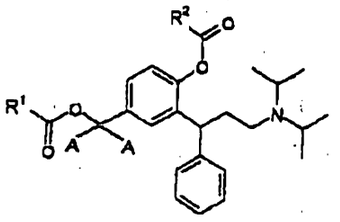


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room tempera-

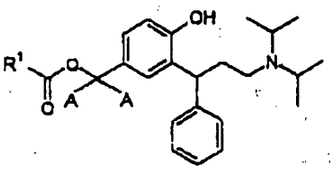
ture and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

The mixed diesters represented by the general formula IV



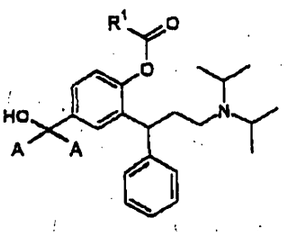
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

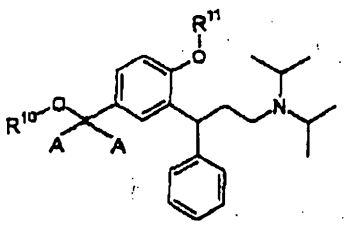


Formula II

as defined hereinbefore.

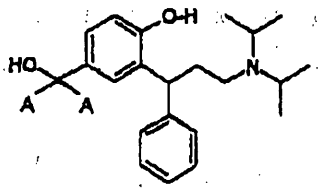
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI



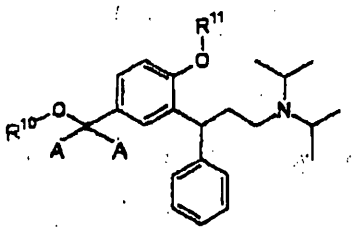
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



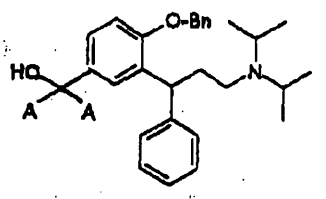
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

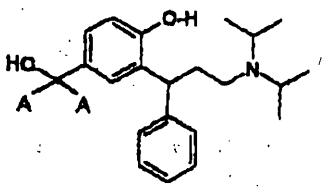


Formula VI

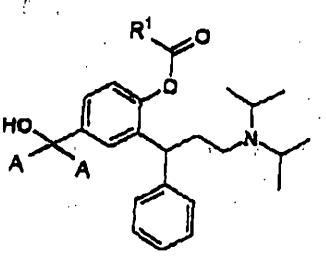
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

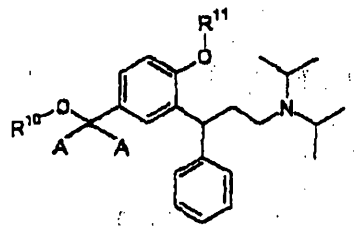


and



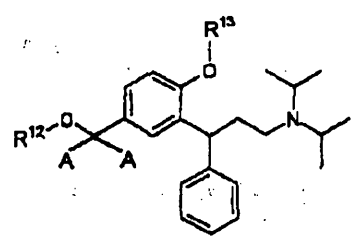
Formula II

or



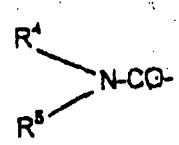
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or



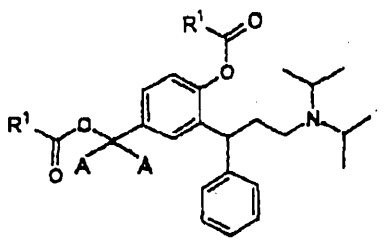
Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

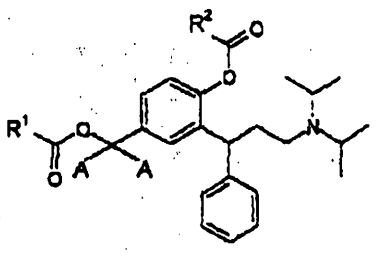


wherein R^4 and R^5 are as defined above

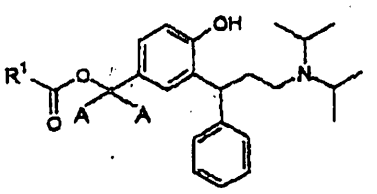
or of benzylic acylates selected from



Formula III



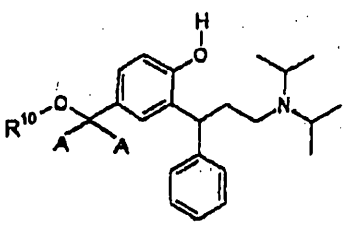
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

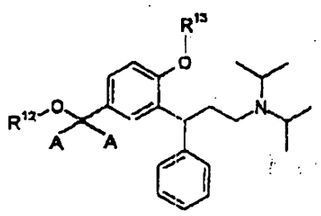


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

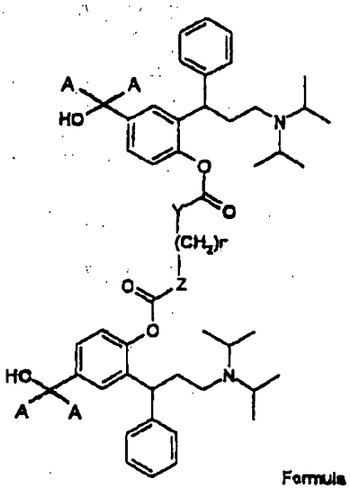
In summary, regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. 53: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. 30: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis 1981, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta 76: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. 26: 4307-4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

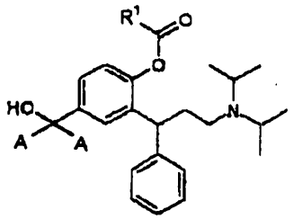


Formula VII

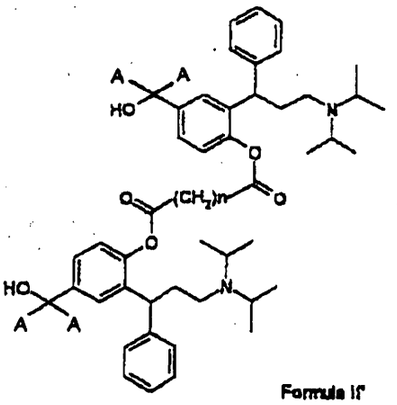


Formula VIII

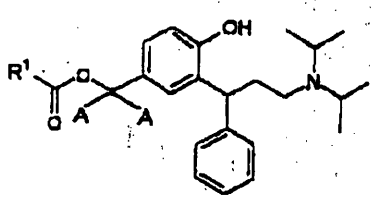
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



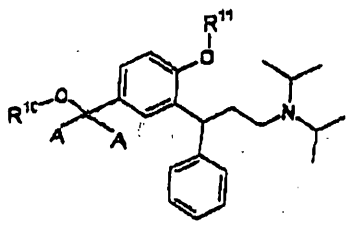
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents $-C(=O)-Y-R^3$, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in

the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^{1}H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.
Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%); (2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).
Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.
Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.
IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.
Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.
Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester
An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at

room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with ethylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one*, m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46,

126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid*, colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, M^+), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly

with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

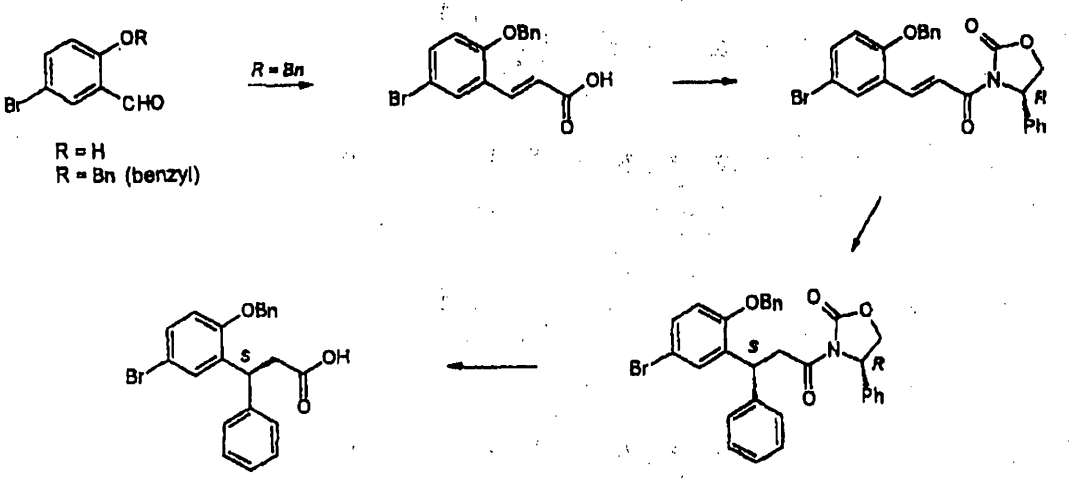
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-

heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) **Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromo-benzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid

material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

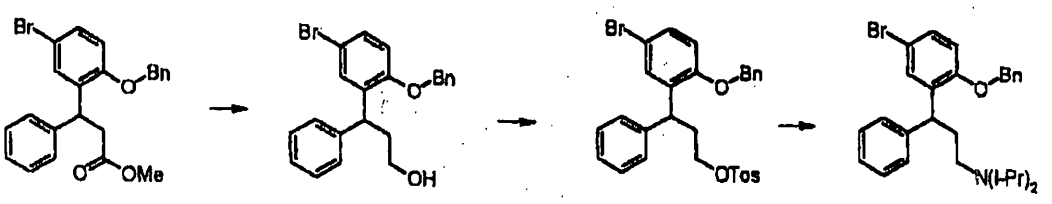
HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Conjugate organocuprate addition of phenylmagnesiumbromide to *3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystalliza-

tions, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) **Synthesis of the R- and S- Enantiomers of Intermediate B**

(i) **Phenylpropanol Route**



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

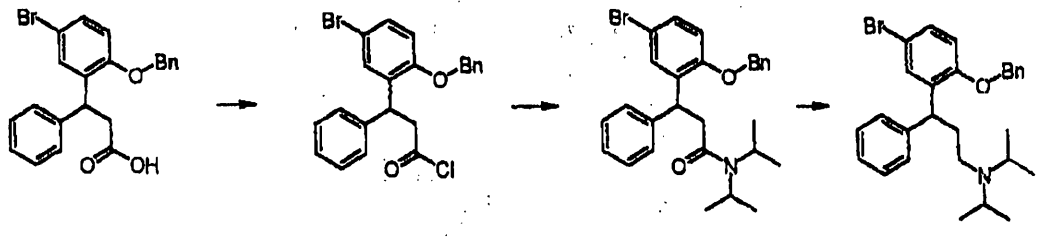
A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9%

yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temper-

ature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionamide

The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diiso-propylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc:(4) 0.86. The NMR spectrum corresponds to the product, obtained from the

tosylate precursor (see above).

S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

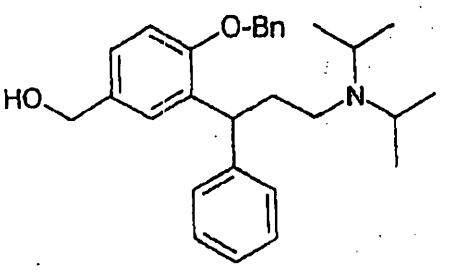
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to

pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n = 2)

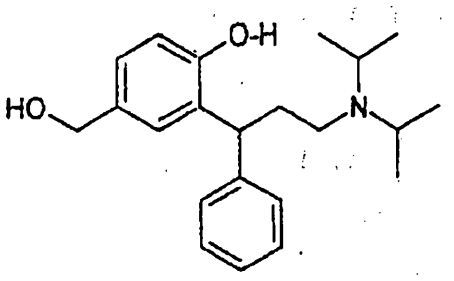
Repetition of the above described reduction of the methylester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

Intermediate B (n = 1)

A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.

Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *S-(-)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield,

colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).

R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.

S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

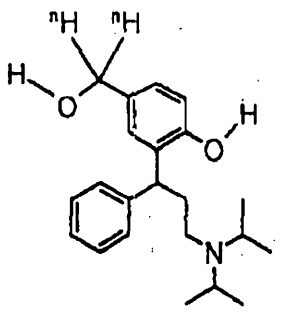
Intermediate d_2-B (n = 2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc: (4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



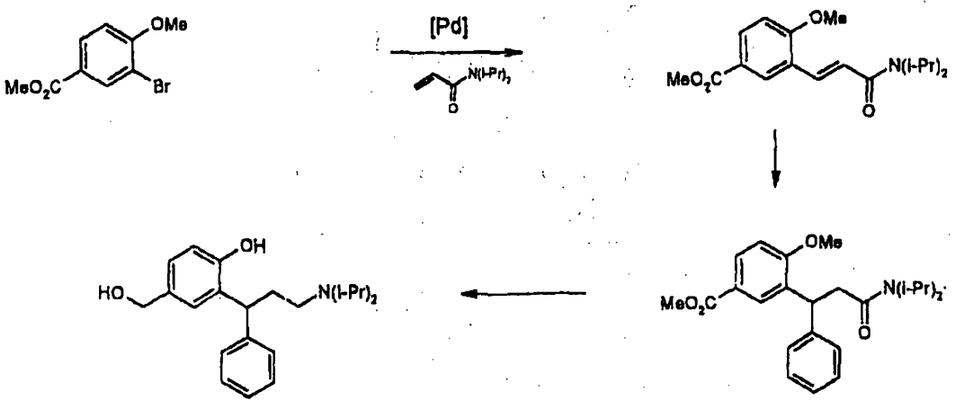
Intermediate d_2-B

n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) Heck-Cuprate-Route to Intermediate B



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were

dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40.

NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07.

MS (EI, DI, 105°C): 319 (M^+, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclo-

hexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave

(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

as a viscous slightly yellow syrup (1.8 g, 44% yield).
NMR (CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C): 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room tem-

perature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of **S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate**

in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:
(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids
A stirred solution of (±)-*2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid mono-chloride for compounds of formula II, 2.50 mmol for compounds

of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.

The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16,

43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI

(ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)

NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%);gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

tlc R_f 0.30 (4); colourless syrup

Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform);

NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.

LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 ($M^{+\cdot}$, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 ($M^{+\cdot}$, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 ($M^{+\cdot}$, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 ($M^{+\cdot}$, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23,

64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.

Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim.* Acta 37: 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethylsilyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$)- 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc: R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76,

148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR (DMSO-d_6): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) **Mixed diesters**

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53,

21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2); NMR ($CDCl_3$): 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

Molar equivalents of bases of formula VI (R^{11} = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethyl-phenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl

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39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-di-methylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropyl-amine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7

(78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$): 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloro-methane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After

washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride
Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72,

130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3); NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

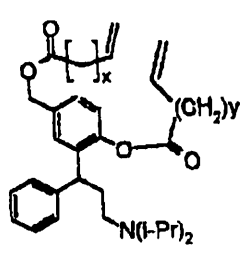
(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N,N-diethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

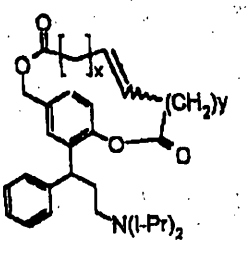
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6); dihydrochloride m.p. 142.5-145.6°C

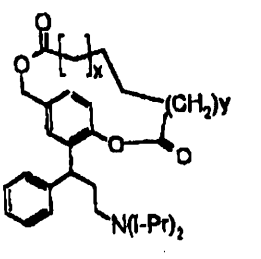
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) **Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)**







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy-*

methyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(f)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the

presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm

CH resonances of the poly-lactyl chain: 5.10-5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.

Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{CH_2}$), 2.40-2.80 ($N\underline{CH_2}$), 3.30-3.50 ($N\underline{CH}$), 4.45-4.55 ($\underline{CH}CH_2$), 4.70-4.80 ($\underline{CH_2}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{CH}$).

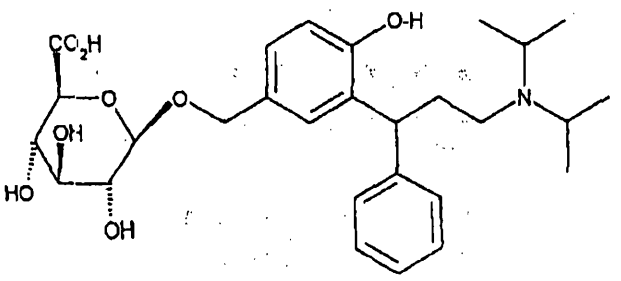
h) **Inorganic ester**

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester
Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) **Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol**
((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropyl-amino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester*, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucurono-syloxymethyl)-phenol, sodium salt,

amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated

for 2 hrs at 37°C with 40 µM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

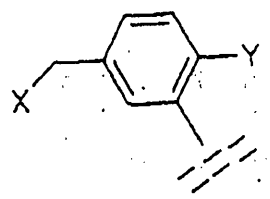
BRIEF DESCRIPTION OF THE DRAWING:

The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:

The prodrugs introduced in the assay show the following chemical structure:



chemical structure	X-/-Y	
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate

iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in

a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(-)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

Different compounds of the invention were tested for their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV de-

tection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24hrs$]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

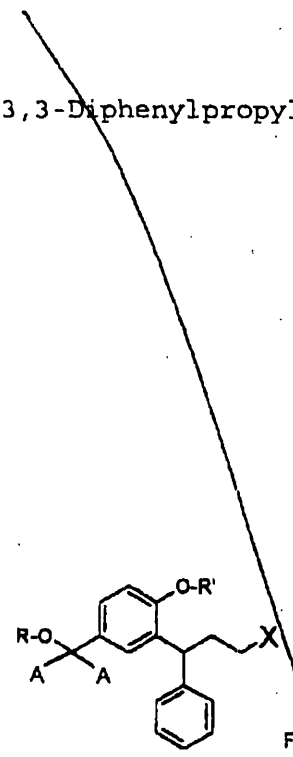
Disubstitution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

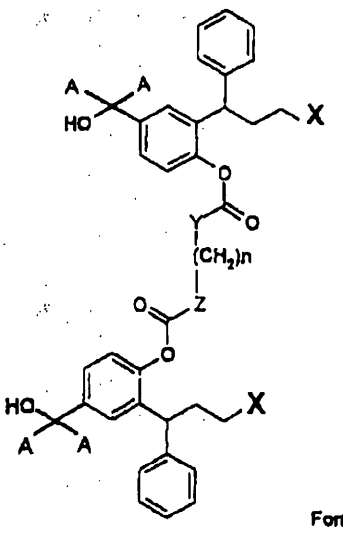
Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



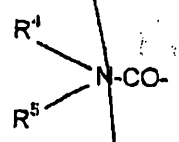
Formula VII'

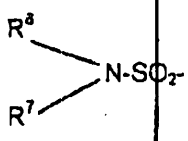
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

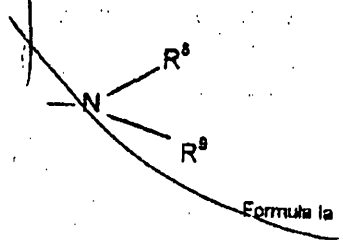
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^5 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

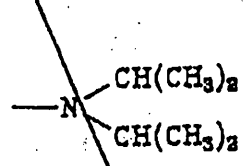
A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

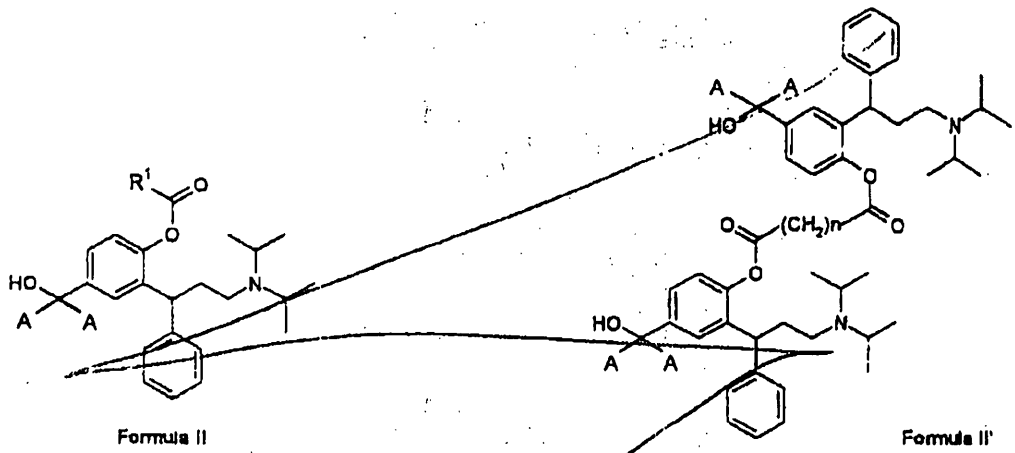
and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

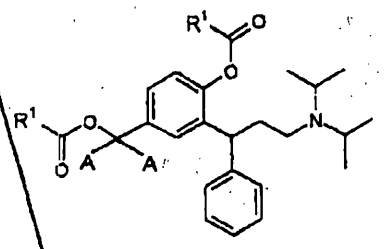
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



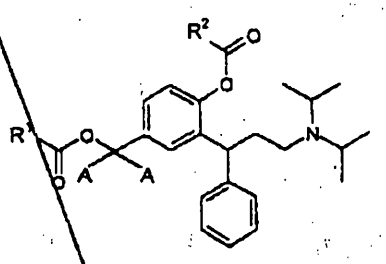
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is defined as in claim 3

and

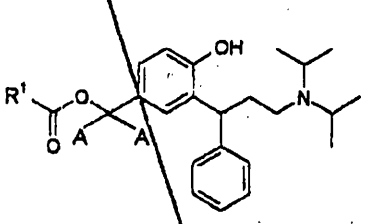
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



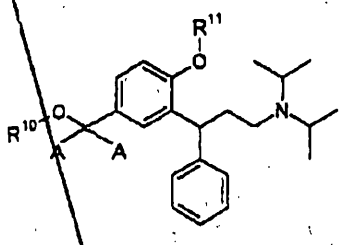
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:
(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

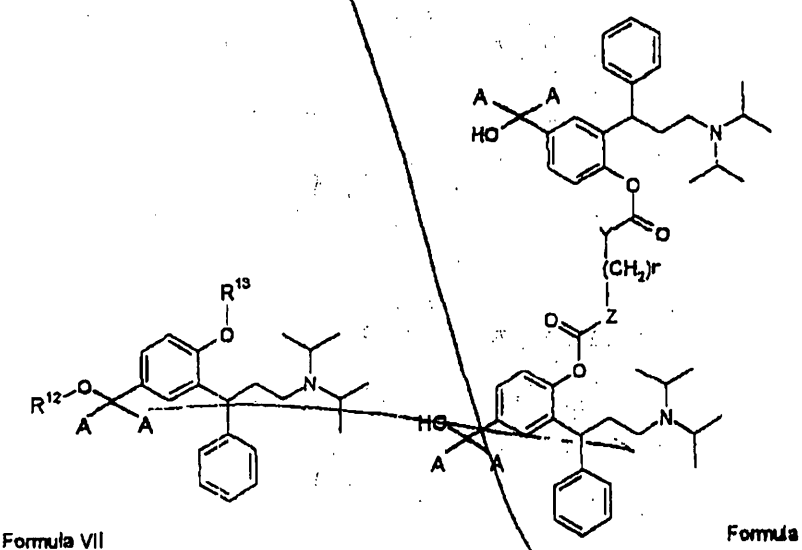
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-tri-methylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

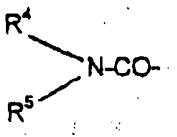
13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII



Formula VII

Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

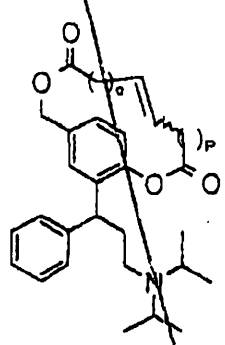
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

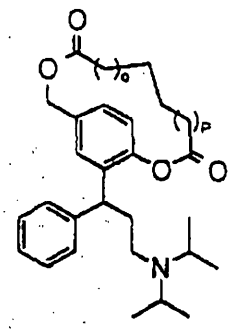
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



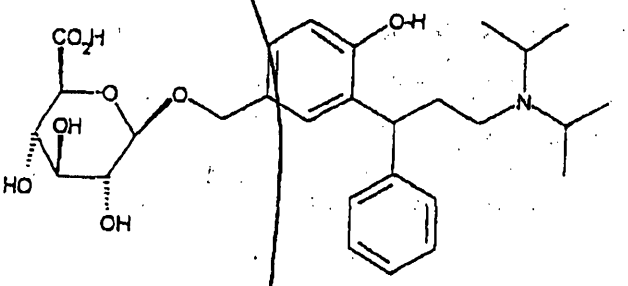
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenyl-propyl)-4-hycroxymethyl-phenol

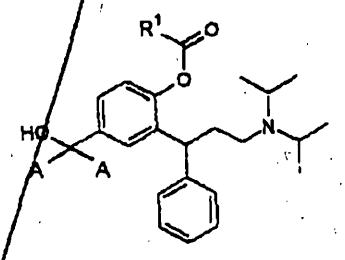
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and

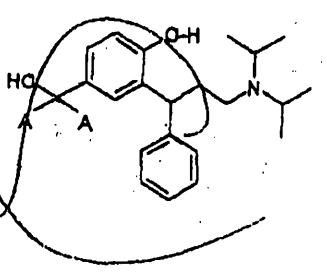
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

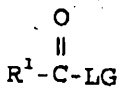


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

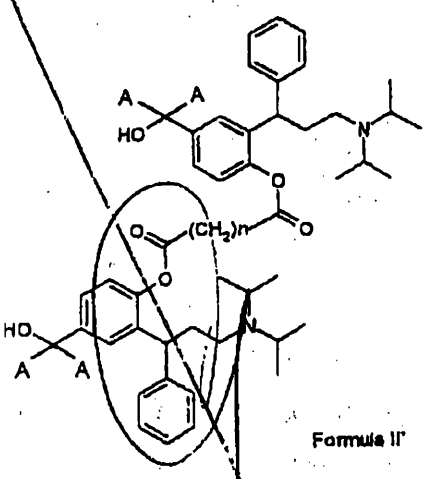


with an equivalent of an acylating agent selected from



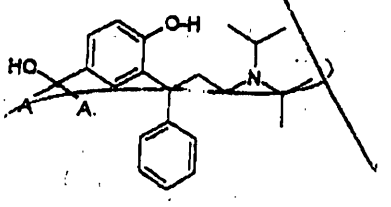
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

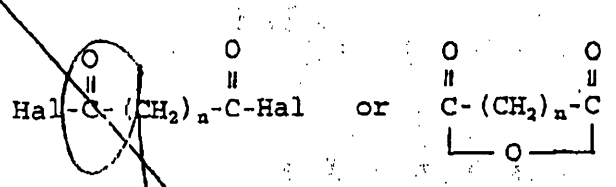


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula

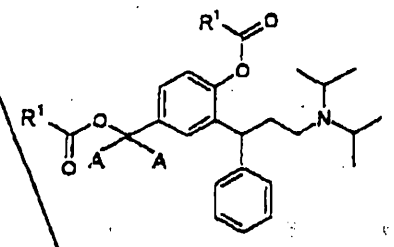


with an acylating agent selected from



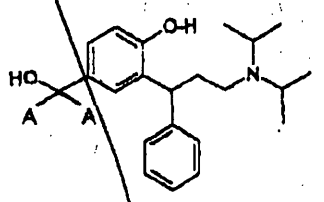
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



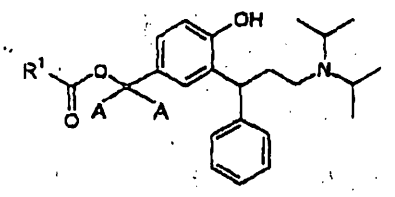
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



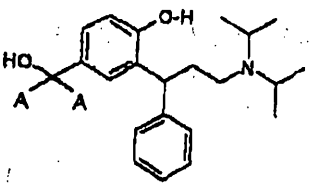
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



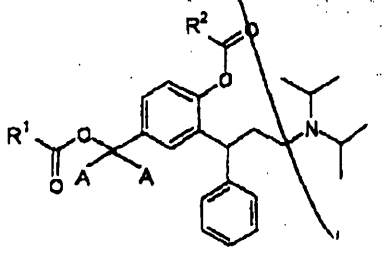
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



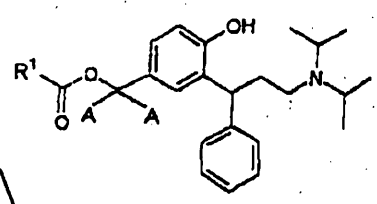
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

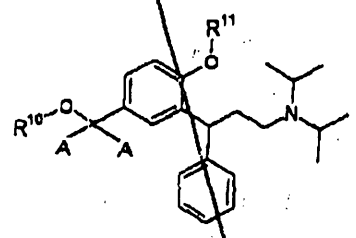
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

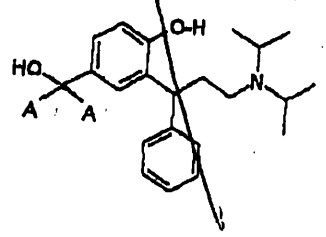
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



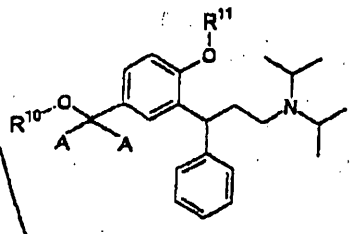
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



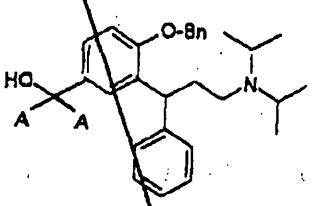
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

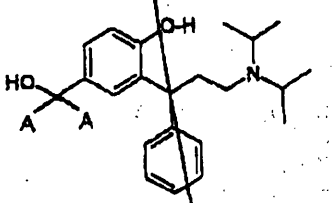


Formula VI

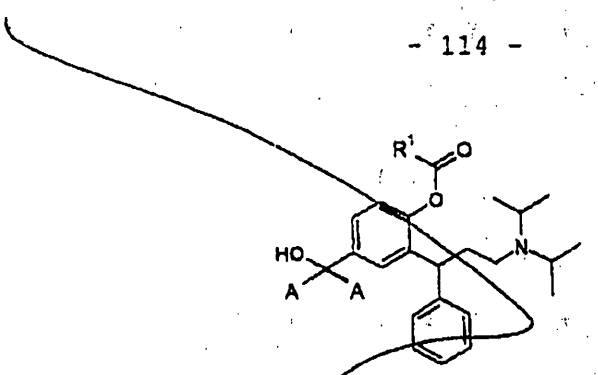
wherein R^{10} and R^{11} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

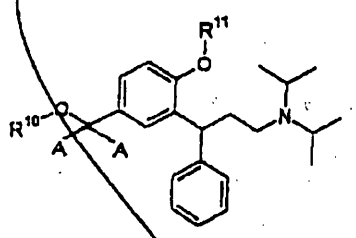


and



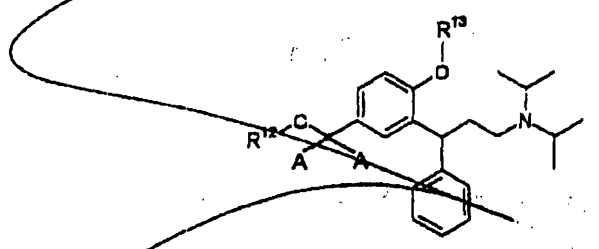
Formula II

or



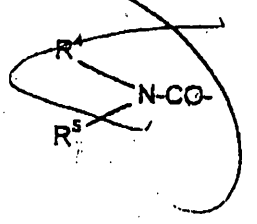
Formula VI

wherein R^{10} is hydrogen or

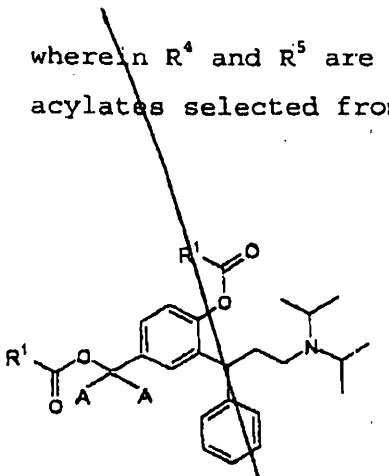


Formula VII

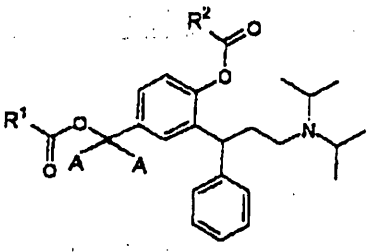
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



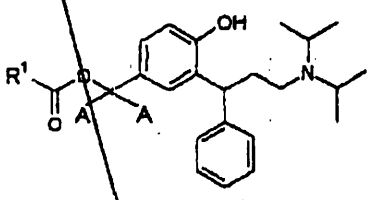
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



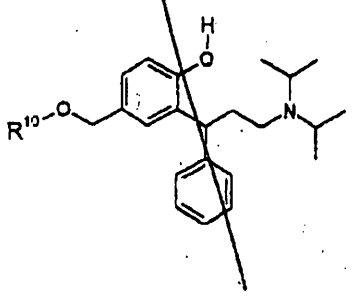
Formula IV



Formula V

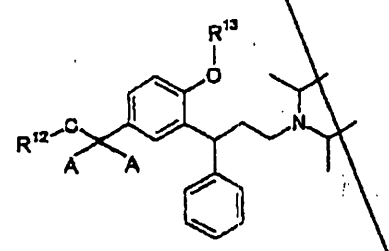
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

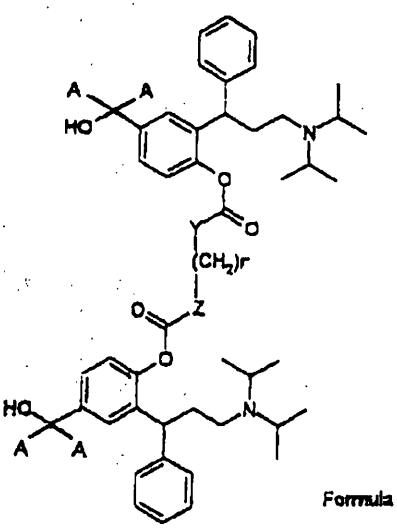


with an alkylating agent selected from alkyl halcgenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

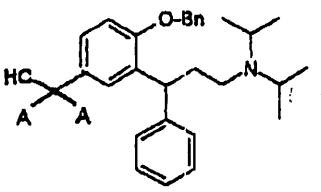


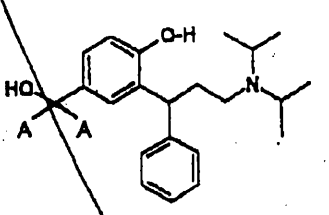
Formula VII

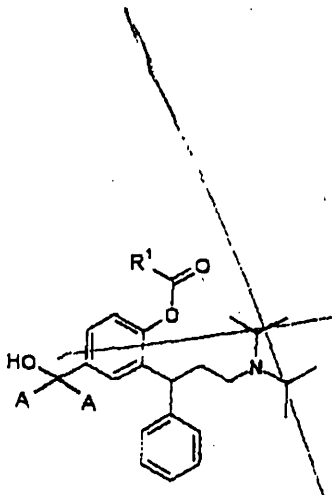


Formula VIII

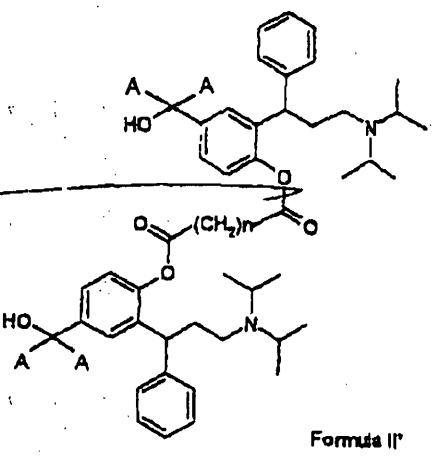
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



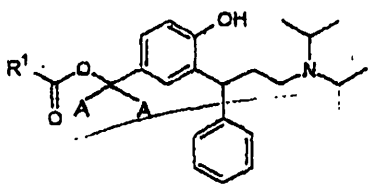




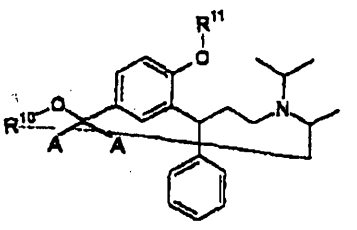
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

.TENT COOPERATION TREA. Y

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
10022/um		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03212	11/05/1999	12/05/1998
International Patent Classification (IPC) or national classification and IPC C07C1/00		
Applicant SCHWARZ PHARMA AG.et.al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 34 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/06/1999	26.07.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gerzain, M Telephone No. +49 89 2399 2128

Form PCT/IPEA/409 (cover sheet) (January 1994) SR22429, 21.07.2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/03212

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-4,7,11-32, 37-94	as originally filed			
5,6,8-10,33-36	as received on	28/04/2000	with letter of	28/04/2000

Claims, No.:

1-27	as received on	28/04/2000	with letter of	28/04/2000

Drawings, sheets:

1/1	as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations

see separate sheet

D1 WO 94 11337
D2 WO 89 06644
D3 L. Nilvebrant et al., European J. of Pharm., vol.327, 195-207 (1997)

Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

All the inconsistencies between the description and claims were corrected (letter of 28/04/00). These amendements do not contravene to Article 34(2)b)PCT and are accordingly allowable.

Novelty - Article 33(2) PCT

The intermediates A (R = H and R' = $CH_2\phi$) and B (R = R' = H) are 3,3-diphenylpropylamines of D1, which are excluded from the present application. They are used as starting materials to synthesize the compounds of the invention.

The 3,3-diphenylpropylamines of D2 do not possess a protected hydroxymethyl group on the 5-position of the 2-hydroxyl-phenyl group.

The antimuscarinic properties of tolterodine (R' = H; Me instead of CA_2-O-R), oxybutinin and atropine are compared in D3.

The subject-matter of claims 1-15 could therefore be considered as novel in view of D1, D2 or D3. The processes to prepare such novel compounds (claims 16-24), the compositions containing them (claim 26) and their use (claims 25 and 27) could accordingly be considered as novel.

Inventive step- Article 33(3) PCT

3,3-Diphenylpropylamines of D1 where R = H and R' = H, Me, $CH_2\phi$ (pages 12-13 and claims 5-6) are excluded from the present demand (claim 1, page 96). The technical problem is to provide other antimuscarinic agents with increased penetrating property through biological membrane. The solution of the applicant are the 3,3-

diphenylpropylamine derivatives (I) and (VII') (claim 1).

The active metabolite formed from the 3,3-diphenylpropylamines of **D1** are used for urge incontinence. The presence of an additional hydroxy group leads to an increased hydrophilic property of these compounds, resulting in a lower absorption. This could be outlined *via* a comparison between the intermediate B (**D1**) and the derivatives of the invention (page 94, Table). The compounds of the invention have also a reduced affinity to bind to muscarinic receptors (page 92, Table). They are consequently solutions of the present technical problem. Nothing in **D1** would have lead the man skilled in the art to derivatize preferentially at the phenolic hydroxyl moiety. An inventive step could therefore be acknowledged for claims 1-15.

An inventive step could also be recognized to the processes of making such novel and inventive compounds (claims 16-24), involving the derivatization of the hydroxy phenolic moiety, the compositions containing them (claim 26) and their use (claims 25 and 27).

09/700094

Express Mail No. EL602856070US

529 Rec'd PCT/PTC 08 NOV 2000

PATENT

#5 5-2-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. MBHB00,1121)

In application of:)
)
Meese and Sparf)
)
Serial No. U.S. National Phase of PCT/EP99/03212)
) Group Art Unit: TBA
Filed: October 19, 2000)
)
For: Novel Derivatives of 3,3-Diphenylpropylamines)

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

- DUPLICATE -
- PTO-1449 -

Dear Sir:

Pursuant to 37 C.F.R. Section 1.97 - 1.99, the Applicant wishes to make the following references of record in the above-identified application. This Information Disclosure Statement is in compliance with the continuing duty of candor as set forth in 37 C.F.R. Section 1.56. Copies of the references cited below are enclosed. These references are also listed on the enclosed PTO Form 1449.

In the judgment of the undersigned, portions of the listed references may be material to the Examiner's consideration of the presently pending claims. This statement is not a representation that the listed references have effective dates early enough to be "prior art" within the meaning of 35 U.S.C. Section 102 or Section 103.

1. International Patent No. WO 94/11337, published May 26, 1994
2. International Patent No. WO 89/06644, published July 27, 1989
3. Nilvebrant et al., (1997) *European Journal of Pharmacology*, Vol. 327, pp. 195-207

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff

Date: November 8, 2000 By: Michael S. Greenfield
Michael S. Greenfield
Reg. No. 37,142

press Mail No. EL602856070US

09/700094

Form PTO-1449

U S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

529 Rec'd PCT/PTC 08 NOV 2000

Atty. Docket No.	Serial No.
MBIIB00,1121	TBA
Applicant: Meese and Sparf	
Filing Date: October 19, 2000	Group: TBA

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	1	WO 94/11337	5/26/94	PCT				
	2	WO 89/06644	7/27/89	PCT				

OTHER DOCUMENTS - Including Author, Title, Date, Pertinent Pages, Etc.

	3	Nilvebrant et al., (1997) *European Journal of Pharmacology*, Vol. 327, pp. 195-207

Examiner	Date Considered

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with any communication.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 00,1121)

#69
5-21

In the Application of:	)	
	)	
Meese et al.	)	
	)	**Examiner: TBA**
Serial No.: U.S. National Phase of PCT/EP99/03212	)	
	)	**Group Art Unit: TBA**
Filing Date: Int'l Filing Date: May 11, 1999	)	
	)	
For: Novel Derivatives of 3,3-diphenylpropylmines	)	

PRELIMINARY AMENDENT

Asst. Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Please consider the following amendments and remarks before examination on the merits.

AMENDMENTS

In the claims:

Please cancel claim 17, 25, 26, and 27.

Please amend the claims as follows:

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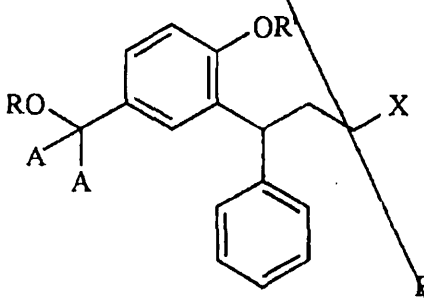
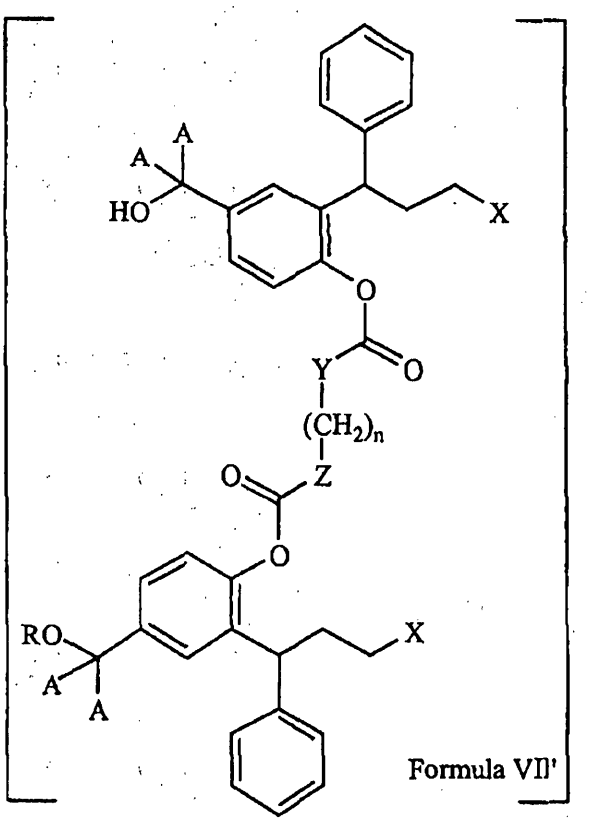
300 South Wacker Drive, 32nd Floor
Chicago, IL 60606
(312)913-0001

1. (Amended) A 3,3-Diphenylpropylamine[s] of the general formula[e] I [and VII']:



Formula I



Formula VII'

wherein R and R´ are independently [selected from]

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; [or]

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl[, preferably benzoyl]; [or]

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

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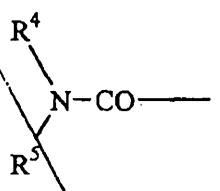
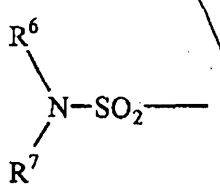
Serial No U S. National Phase of PCT/EP99/03212
Attorney Docket No. 00,1121

d) 

wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, [preferably substituted or unsubstituted phenyl,] benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms [and wherein] or R^4 and R^5 [may] form a ring together with the amine nitrogen; or

e) 

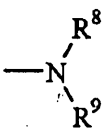
wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, [preferably substituted or unsubstituted phenyl,] benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently [selected from] C_1-C_4 alkyl or aryl, [preferably phenyl,]

with the proviso that R′ is not hydrogen, methyl or benzyl [if] when R is hydrogen, and R is not ethyl [if] when R′ is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent [non-aromatic hydrocarbyl] C_1-C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, [and wherein] or R^8 and R^9 may form a ring together with the amine nitrogen,

[Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,]

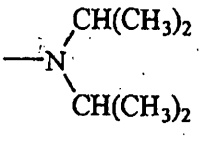
A represents hydrogen (^1H) or deuterium (^2H),

[n is 0 to 12]

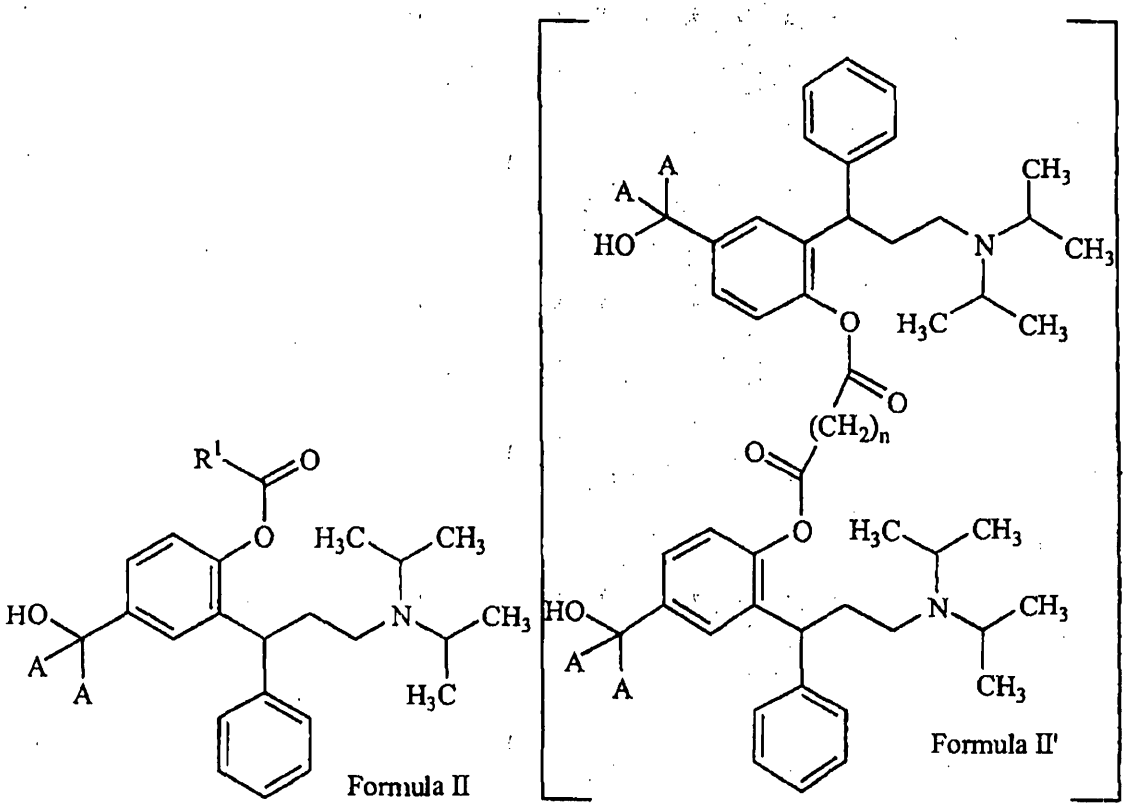
and

their salts with physiologically acceptable acids, their free bases and, when the compounds [can be] are in the form of optical isomers, the racemic mixture and the individual enantiomers.

2. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 1, wherein X is



3. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 2 selected from phenolic monoesters represented by the general formula[e] II [and II']



wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim [3] 2 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

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Serial No. U.S. National Phase of PCT/EP99/03212
Attorney Docket No. 00,1121

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

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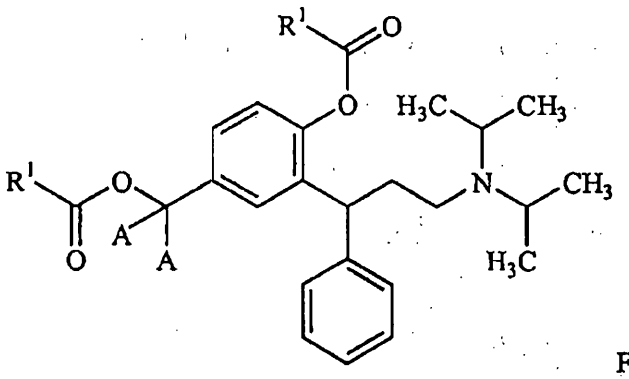
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, and

(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester.

5. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 2 [selected from identical diesters] represented by the general formula III



Formula III

wherein R^1 is [defined as in claim 3] hydrogen, C_1-C_6 alkyl or phenyl.

6. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 5 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,

(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

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(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,

(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

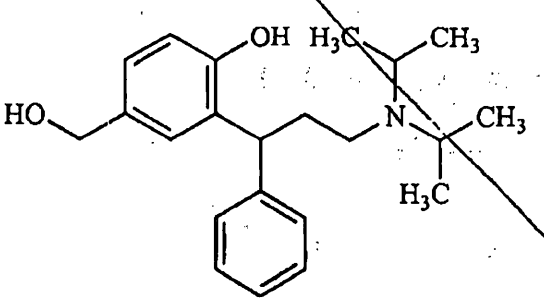
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,

cyclic oct-4-ene-1,8-dioate of Intermediate B,

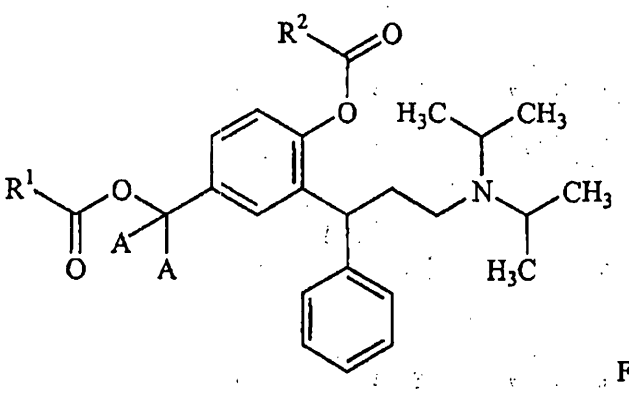
cyclic octane-1,8-dioate of Intermediate B, and

poly-co-DL-lactides of Intermediate B, said Intermediate B having the formula



wherein A is hydrogen (^1H) or deuterium (^2H).

7. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

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wherein R^1 is [defined as in claim 3] hydrogen, C_1-C_6 alkyl or phenyl, and

R^2 represents hydrogen, C_1-C_6 alkyl or phenyl with the proviso that R^1 and R^2 are not identical.

8. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 7 selected from:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,

(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

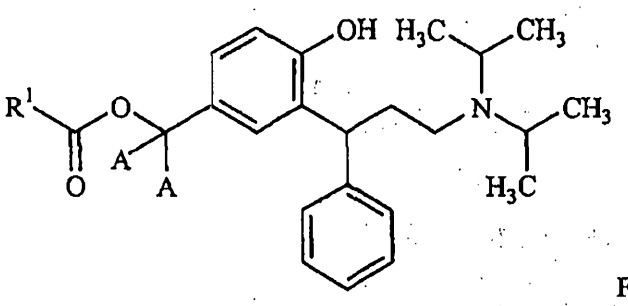
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, and

(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



Formula V

wherein R^1 is [defined as in claim 3] hydrogen, C_1-C_6 alkyl or phenyl.

10. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 9 selected from:

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(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

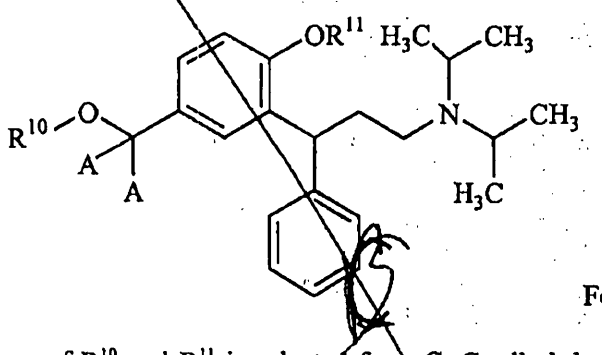
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, and

(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. (Amended) The 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl [or] and $-SiR_aR_bR_c$ [as defined in claim 1] and the other [one] of R^{10} and R^{11} [may additionally] represents hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 11 selected from:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,

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(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,

(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,

(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,

(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,

(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,

(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,

(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,

(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,

(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,

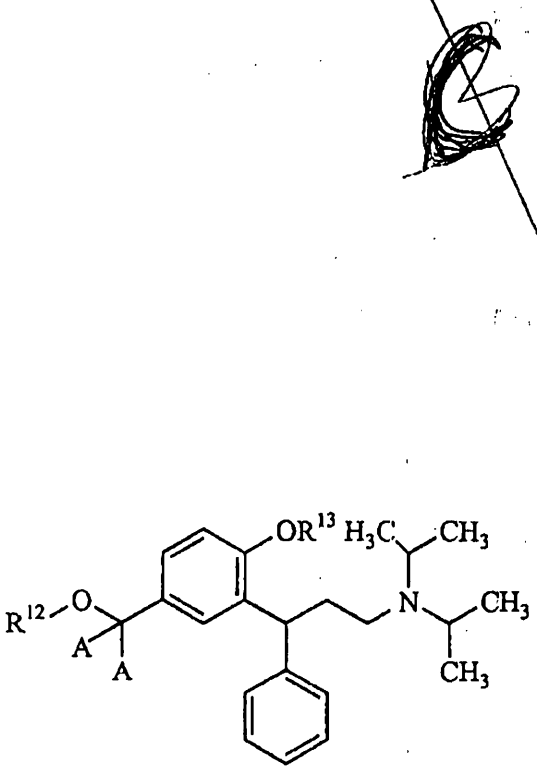
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

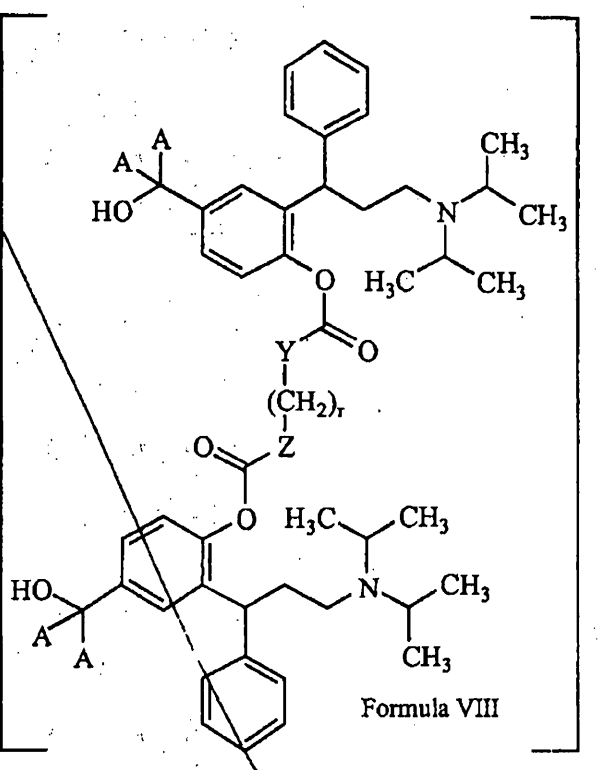
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, and

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

13. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 2 selected from carbonates and carbamates represented by the general formula[e] VII [and VIII]

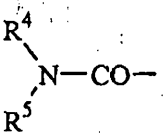


Formula VII



Formula VIII

wherein [Y, Z and n are as defined in claim 1 and wherein] R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



[wherein R^4 and R^5 are as defined in claim 1].

14. (Amended) The 3,3-Diphenylpropylamine[s] as claimed in claim 13 selected from:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxy-benzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

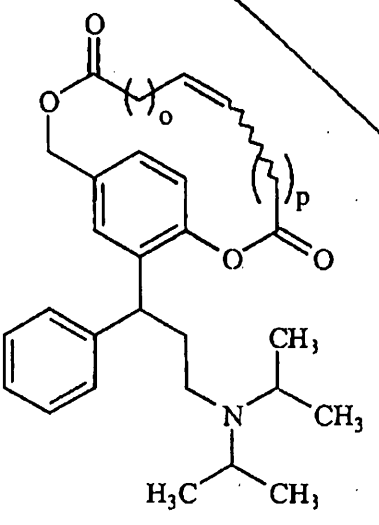
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, and

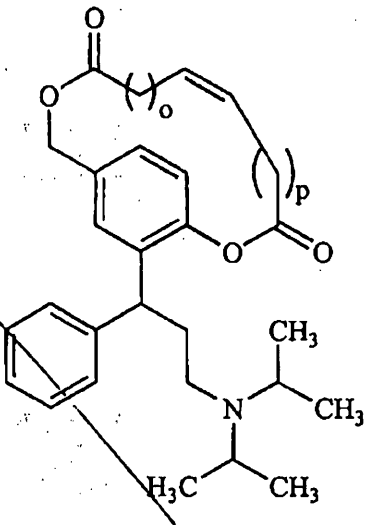
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. (Amended) A 3,3-Diphenylpropylamine[s] selected from

(i) compounds of the formulae IX and IX'



Formula IX



Formula IX'

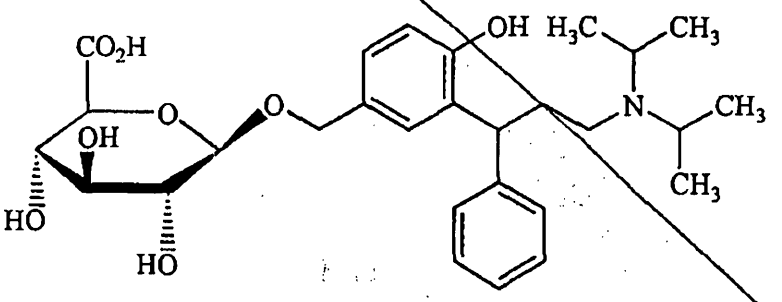
wherein o and p are the same or different and [represent the number of methylene units - CH_2 - and may] range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol

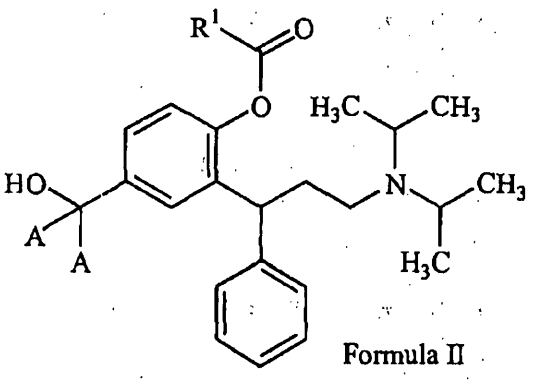
having the formula



and

their salts with physiologically acceptable acids, their free bases and, when the compounds [can be] are in the form of optical isomers, the racemic mixture and the individual enantiomers.

12. 16. (Amended) A process for the production of phenolic monoesters according to claim 3, [represented by the general formula II



Formula II

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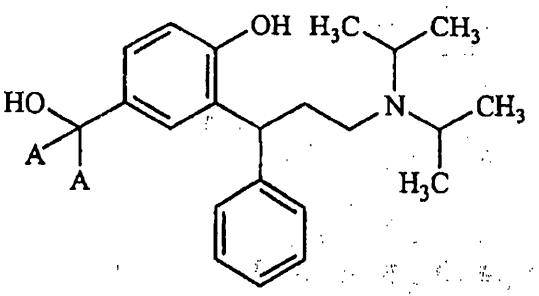
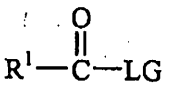
as defined in claim 3,] which comprises treatment of a compound of the formula

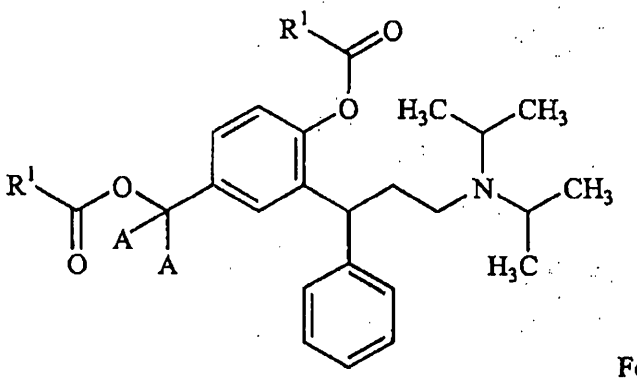


with an equivalent of an acylating agent [selected from] <u>of formula</u>



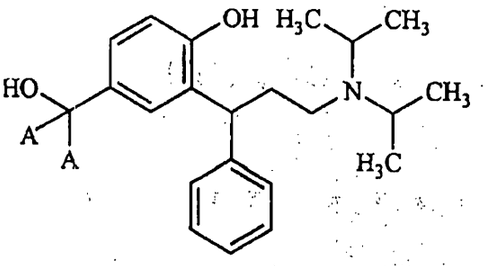
wherein LG represents a leaving group selected from [halogenide] <u>halide</u>, carboxylate and imidazolide [and R^1 is as defined in claim 3,] in an inert solvent in the presence of a [condensating] <u>condensing</u> agent.

18. (Amended) A process for the production of identical diesters <u>according to claim 5,</u> [represented by the general formula III

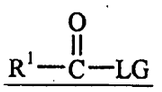


Formula III

as defined in claim 5,] which comprises treatment of a compound of the formula

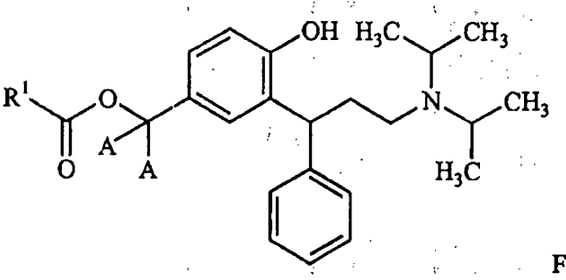


with at least two equivalents of the acylating agent [as defined in claim 16] of formula



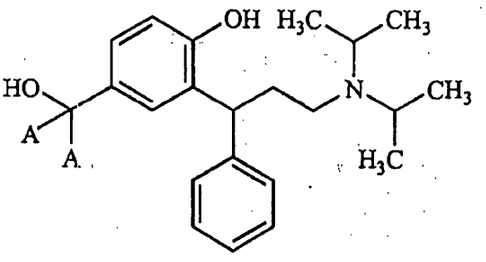
wherein LG represents a leaving group selected from halide, carboxylate and imidazolide in an inert solvent in the presence of a condensing agent.

14 ~~10~~. (Amended) A process for the preparation of benzylic monoesters according to claim 9, [represented by the general formula V



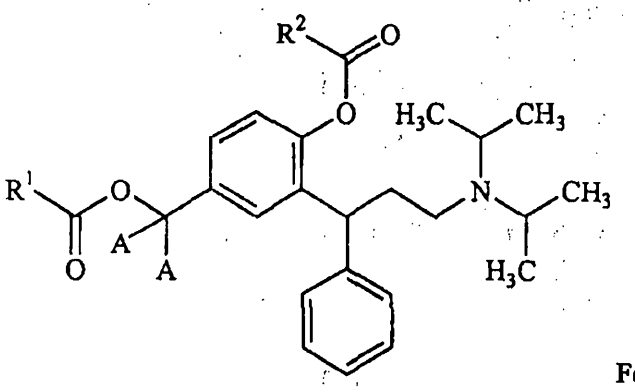
Formula V

as defined in claim 9,] which comprises treatment of a compound of the formula



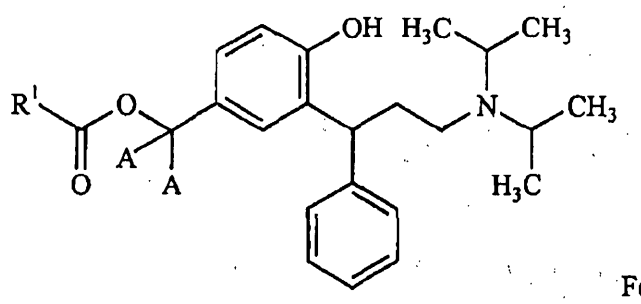
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

15 ~~20.~~ (Amended) A process for the preparation of mixed diesters <u>according to claim 7,</u> [represented by the general formula IV



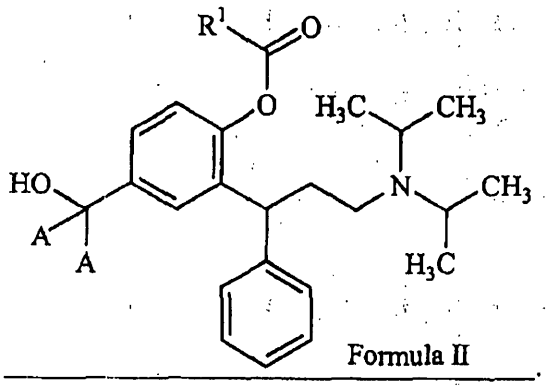
Formula IV

as defined in claim 7,] which comprises acylation of a benzylic monoester represented by the general formula V



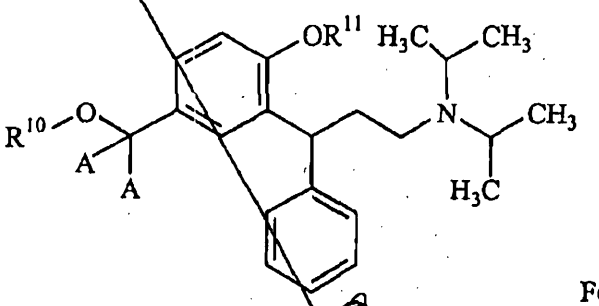
Formula V

[as defined in claim 9] or of a phenolic monoester represented by the formula II [as defined in claim 3]



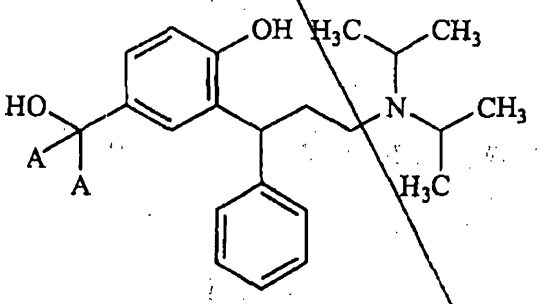
Formula II

21. (Amended) A process for the production of ethers according to claim 11, [represented by the general formula VI



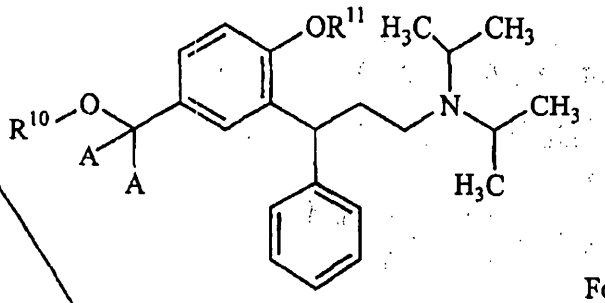
Formula VI

as defined in claim 11] wherein R^{11} is hydrogen, which comprises reacting a compound of the formula



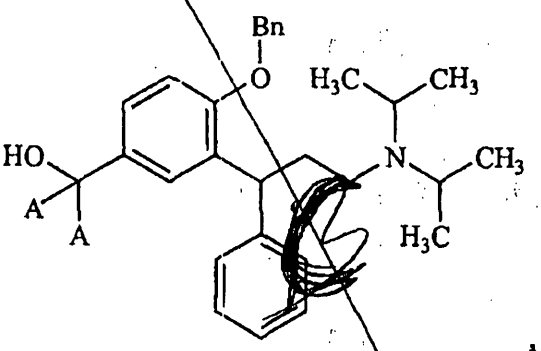
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. (Amended) A process for the preparation of ethers according to claim 11, [represented by the general formula VI



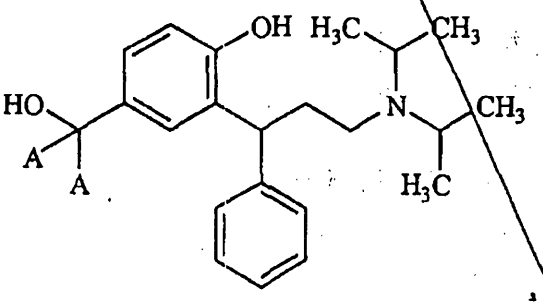
Formula VI]

wherein R^{10} and R^{11} are as defined in claim 11,] which comprises acid or base treatment, in the presence of suitable hydroxy reagents, of [free benzylic alcohols] a compound selected from



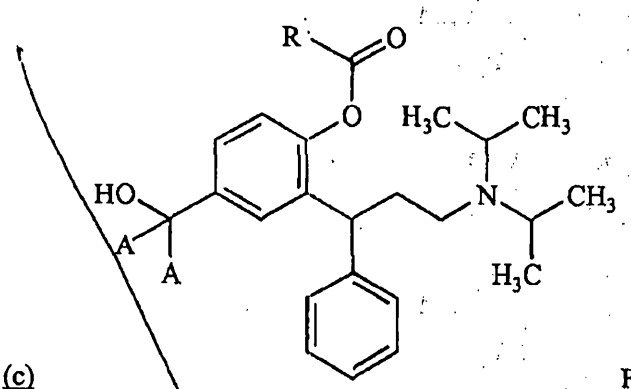
(a)

[and]



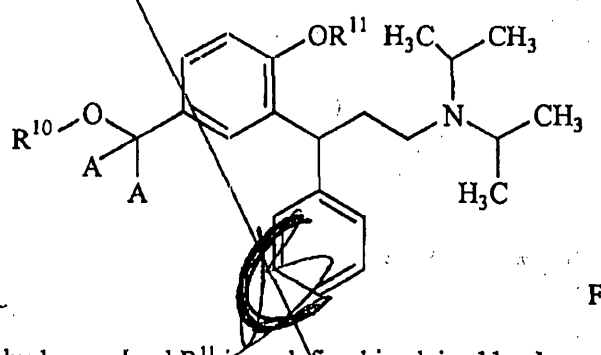
(b)

[and]



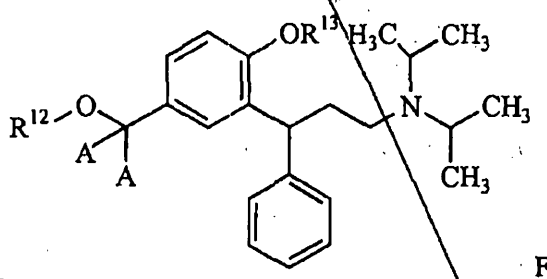
(c) Formula II,

[or]



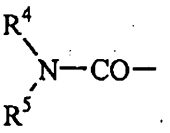
(d) Formula VI

wherein R^{10} is hydrogen [and R^{11} is as defined in claim 11 or],



(e) Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



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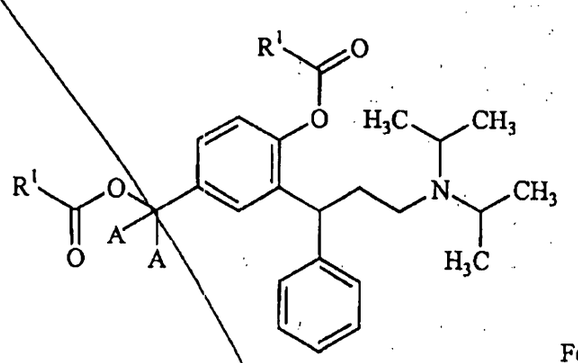
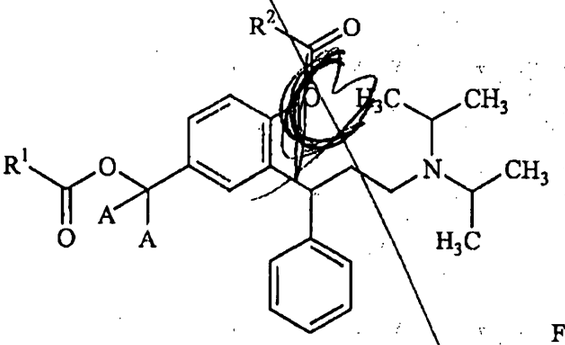
wherein R^4 and R^5 [are as defined in claim 1] independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms or R^4 and R^5 form a ring together with the amine nitrogen, [or of] and

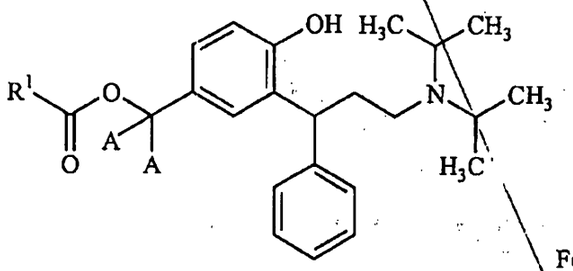
(f) benzylic acylates selected from



Formula III,



Formula IV, and



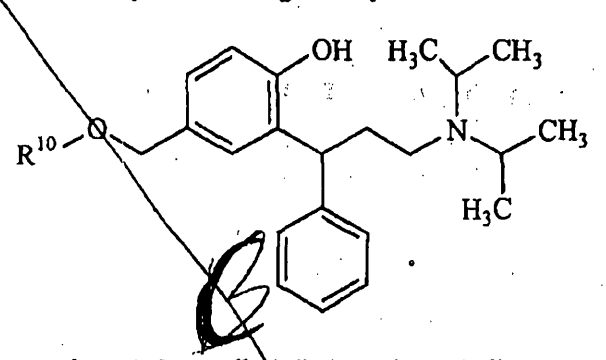
Formula V,

[wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.]

wherein R^1 is hydrogen, C_1-C_6 alkyl or phenyl, and R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

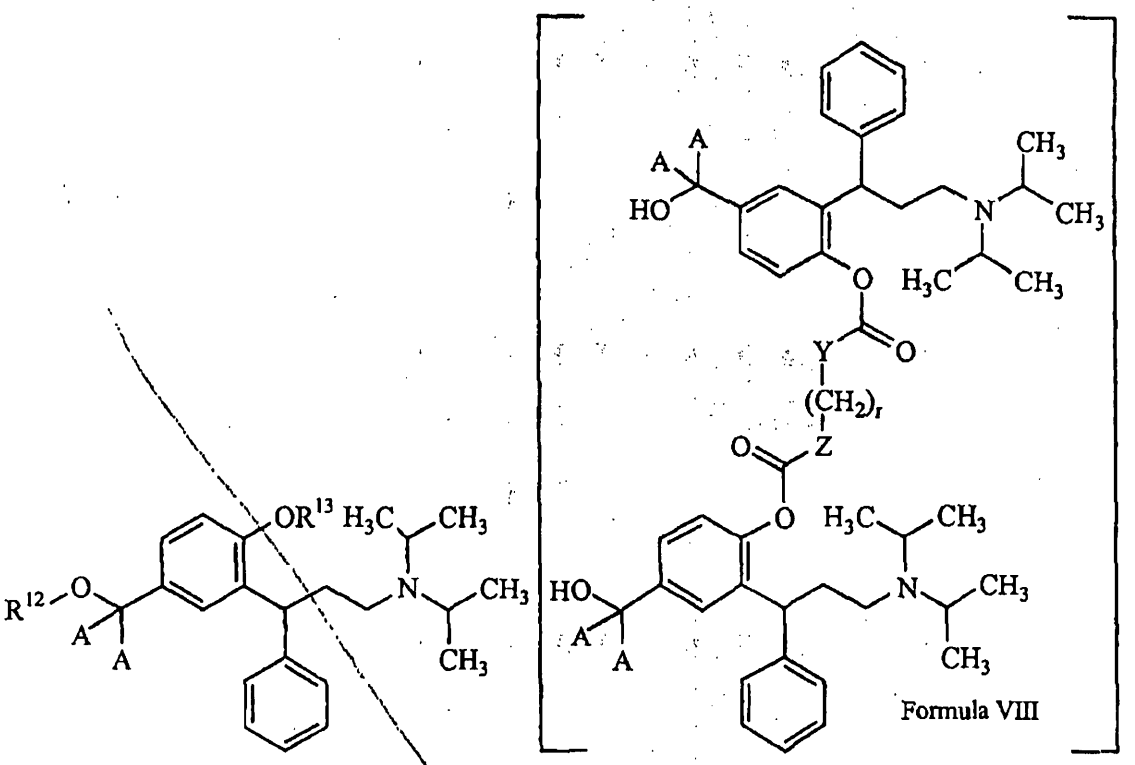
with the proviso that R^1 and R^2 are not identical.

23. (Amended) A process for the preparation of ethers of formula VI [as defined in] according to claim 11, which comprises treating a compound of the formula



with an alkylating agent selected from alkyl [halogenides] halides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

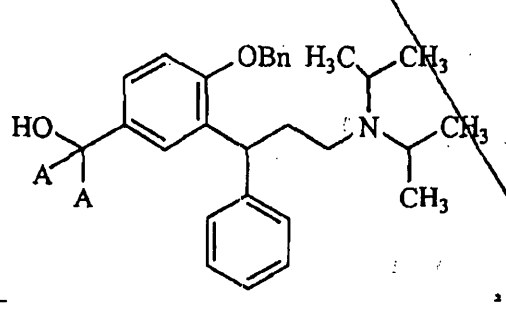
24. (Amended) A process for the preparation of carbonates and carbamates according to claim 13 [represented by the general formulae VII and VIII



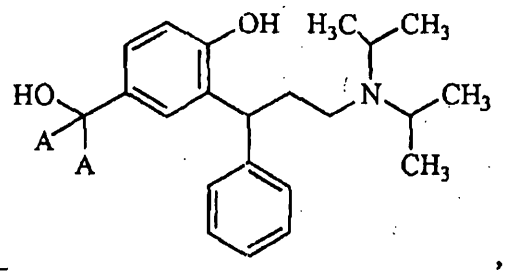
Formula VII

Formula VIII

as defined in claim 13,] which comprises reacting a compound selected from the group consisting of



(a)



(b)

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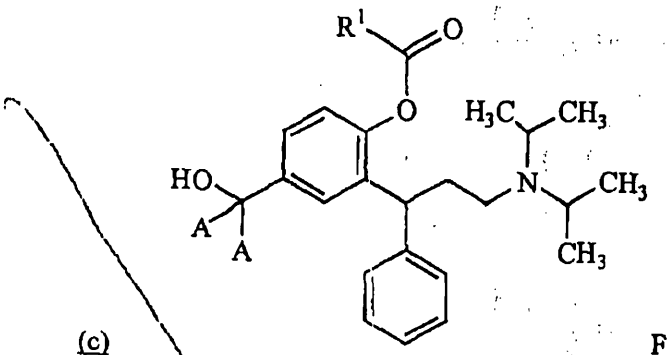
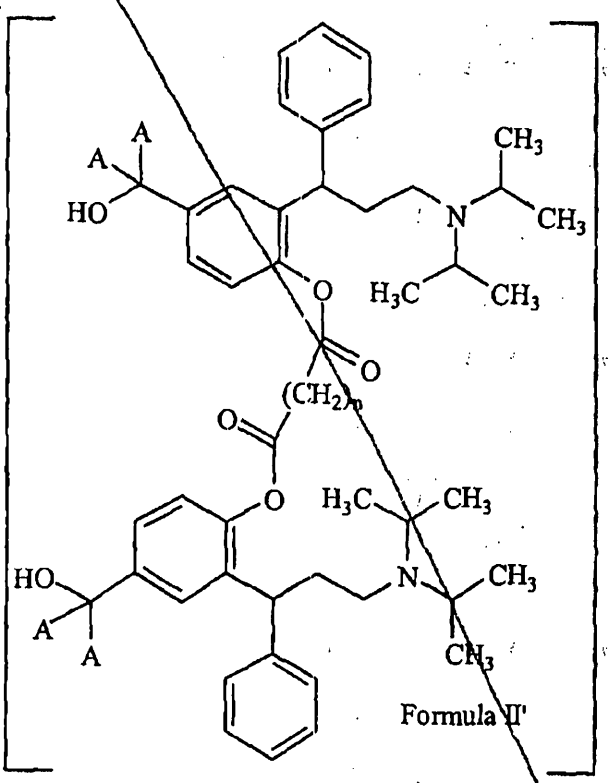
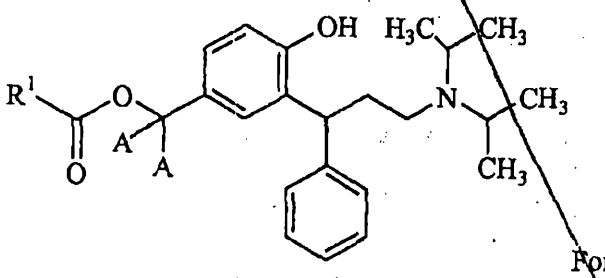


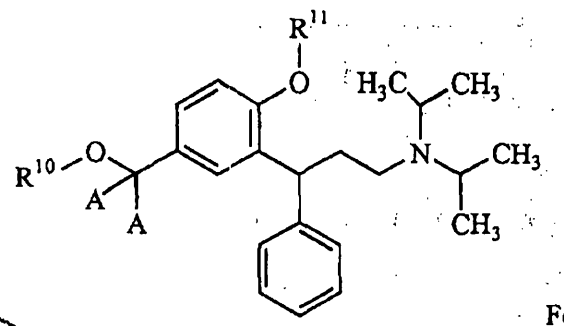
(c) Formula II,



Formula II'



(d) Formula V, and



(e) Formula VI,

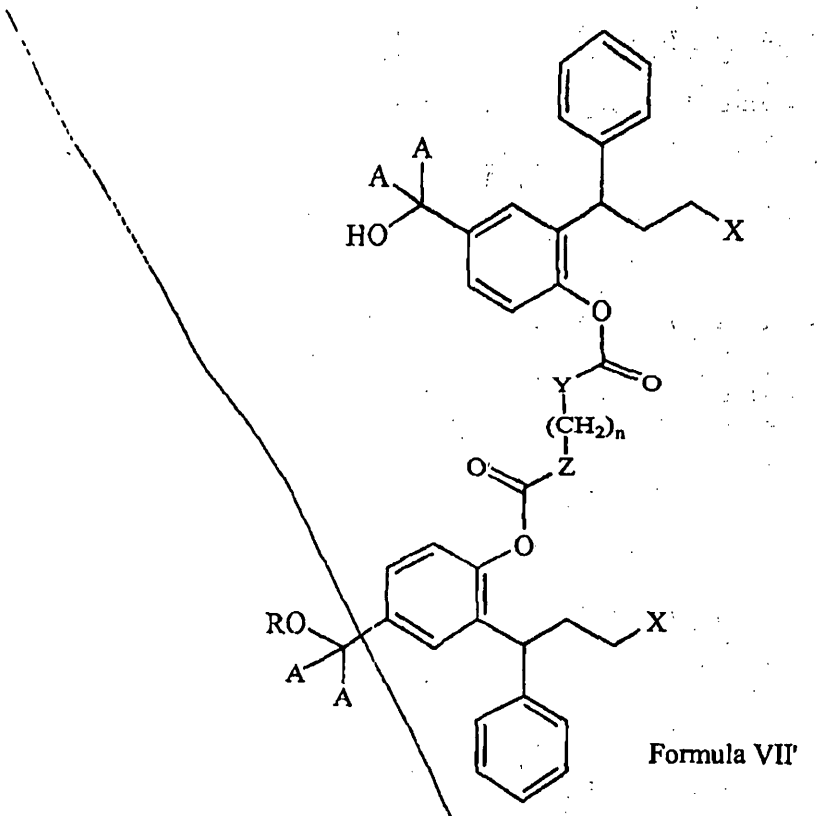
wherein R^1 [is defined as in claim 3] represents hydrogen, C_1-C_6 alkyl or phenyl, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is [as defined in claim 11] C_1-C_6 alkyl, benzyl, $-SiR_aR_bR_c$ hydrogen, C_1-C_6 alkylcarbonyl or benzoyl, wherein R_a, R_b, R_c are independently C_1-C_4 alkyl or aryl,

with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

Please add the following new claims:

28. A 3,3-Diphenylpropylamine of the general formula VII':

Sub B8



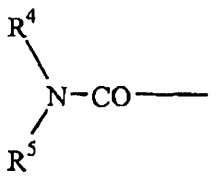
Formula VII'

wherein R is

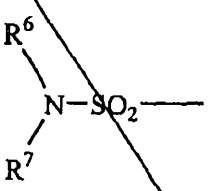
a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently

represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

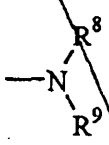
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl,

with the proviso that R′ is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R′ is hydrogen,

X represents a tertiary amino group of formula Ia


Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

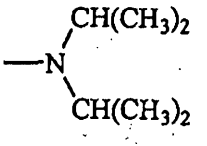
A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12, and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

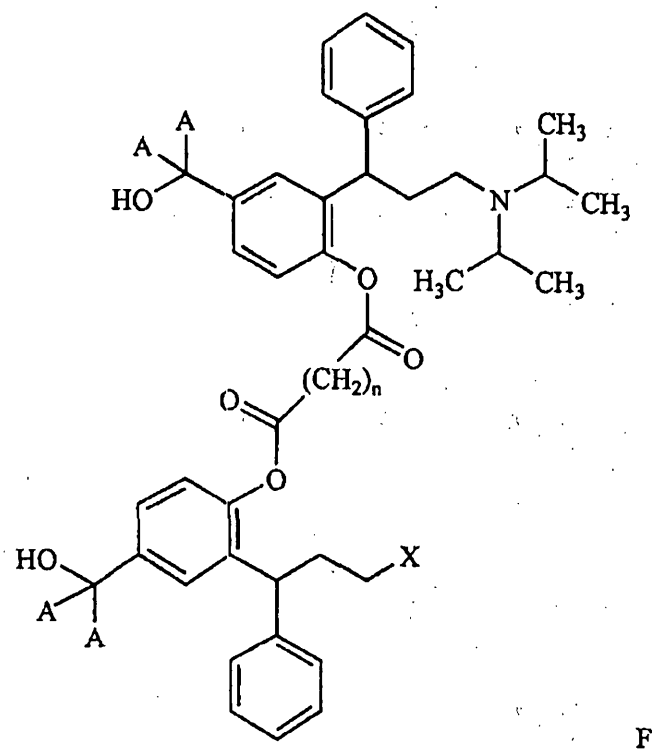
16

17 ~~29~~ The 3,3-Diphenylpropylamines as claimed in claim ~~28~~, wherein X is



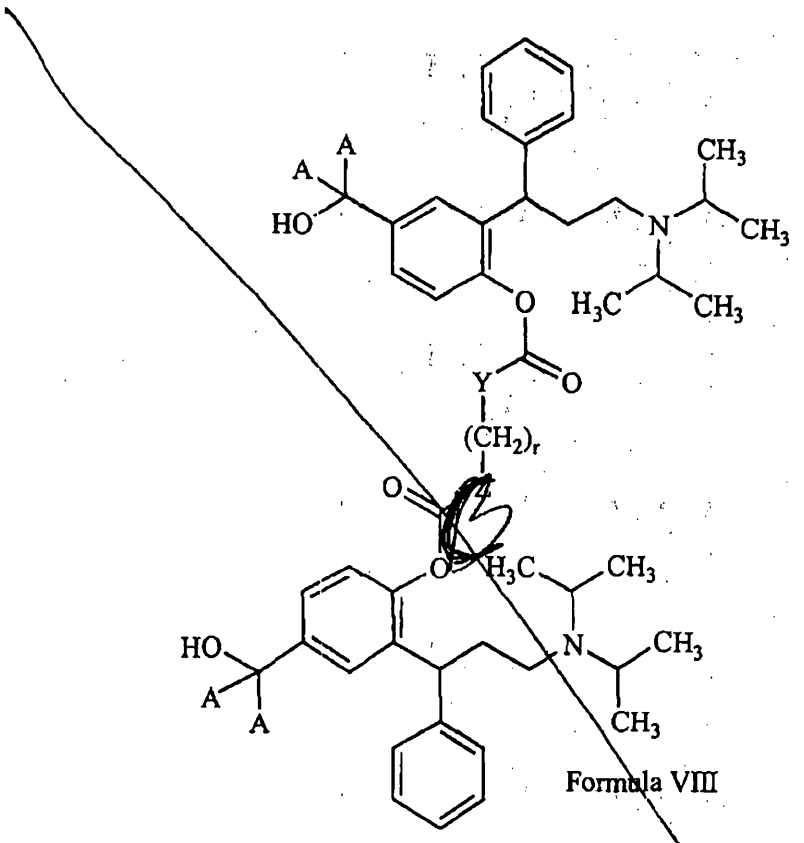
17

18 ~~30~~ The 3,3-Diphenylpropylamine as claimed in claim ~~29~~ selected from phenolic monoesters represented by the general formula II'



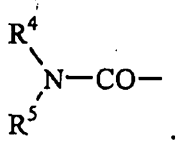
Formula II'.

31. The 3,3-Diphenylpropylamine as claimed in claim 29 selected from carbonates and carbamates represented by the general formula VIII



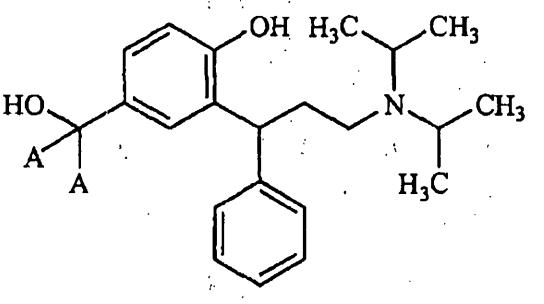
Formula VIII

wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



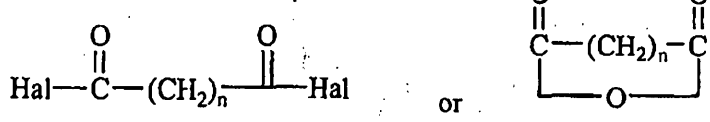
18

19 ~~18~~. A process for the production of phenolic monoesters according to claim ~~30~~, which comprises treatment of two equivalents of a compound of the formula



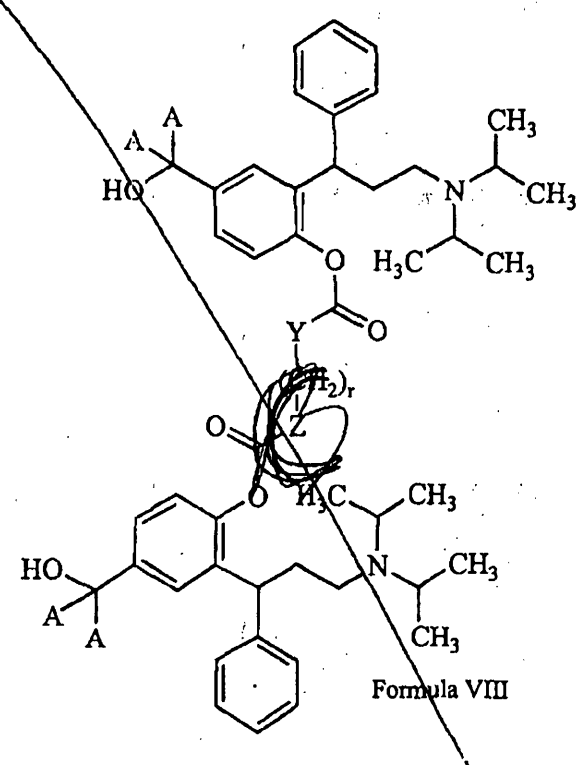
Cont
Q2

with an acylating agent of formula



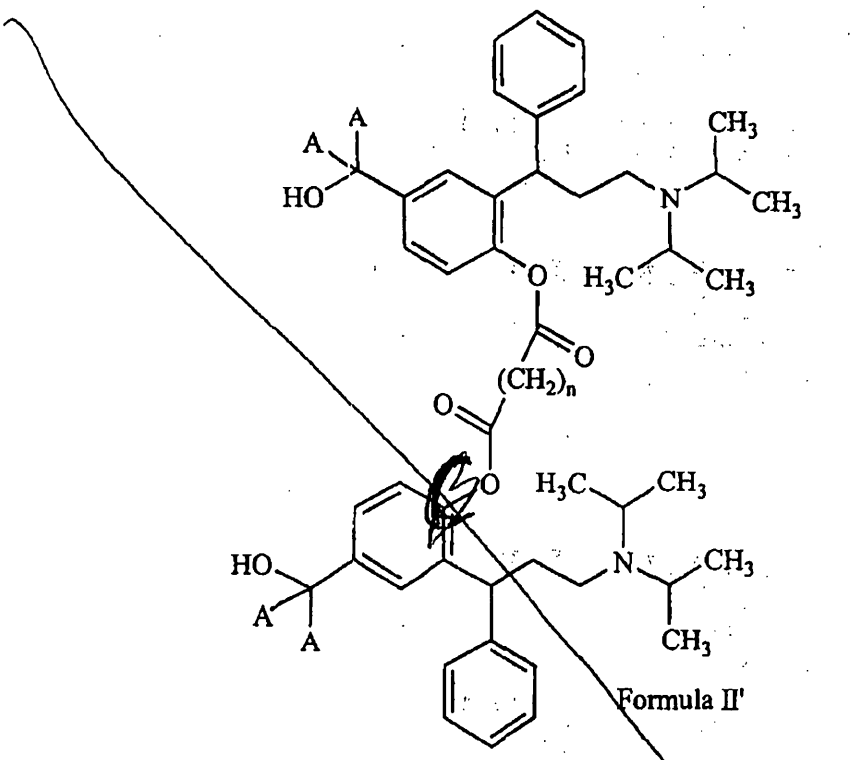
wherein Hal represents a halogen atom.

33. A process for the preparation of carbonates and carbamates according to claim 13



Formula VIII

which comprises reacting a compound of formula



Formula II'

wherein n is 0 to 12, with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

34. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1-15 and 28-31 and a pharmaceutically acceptable carrier.

35. A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims 1-15 and 28-31.

~~22~~36. A method of treating a disease in a mammal that is amenable to treatment by antagonizing muscarinic receptors in the mammal, the method comprising administering an amount of a composition according to claim ~~34~~ 20 effective to diminish or eliminate symptoms of the disease.

~~23~~37. The method according to claim ~~36~~ 22 wherein the disease is urinary incontinence.

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Cont
02

24 ~~38~~. The method according to claim ~~37~~ 23 wherein the mammal is a human.

REMARKS

The amendments presented herein bring the claims into conformance with U.S. practice. No new subject matter has been added. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

Date: November 8, 2000

Michael S. Greenfield
Registration No. 37,142

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Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

FIG. 1

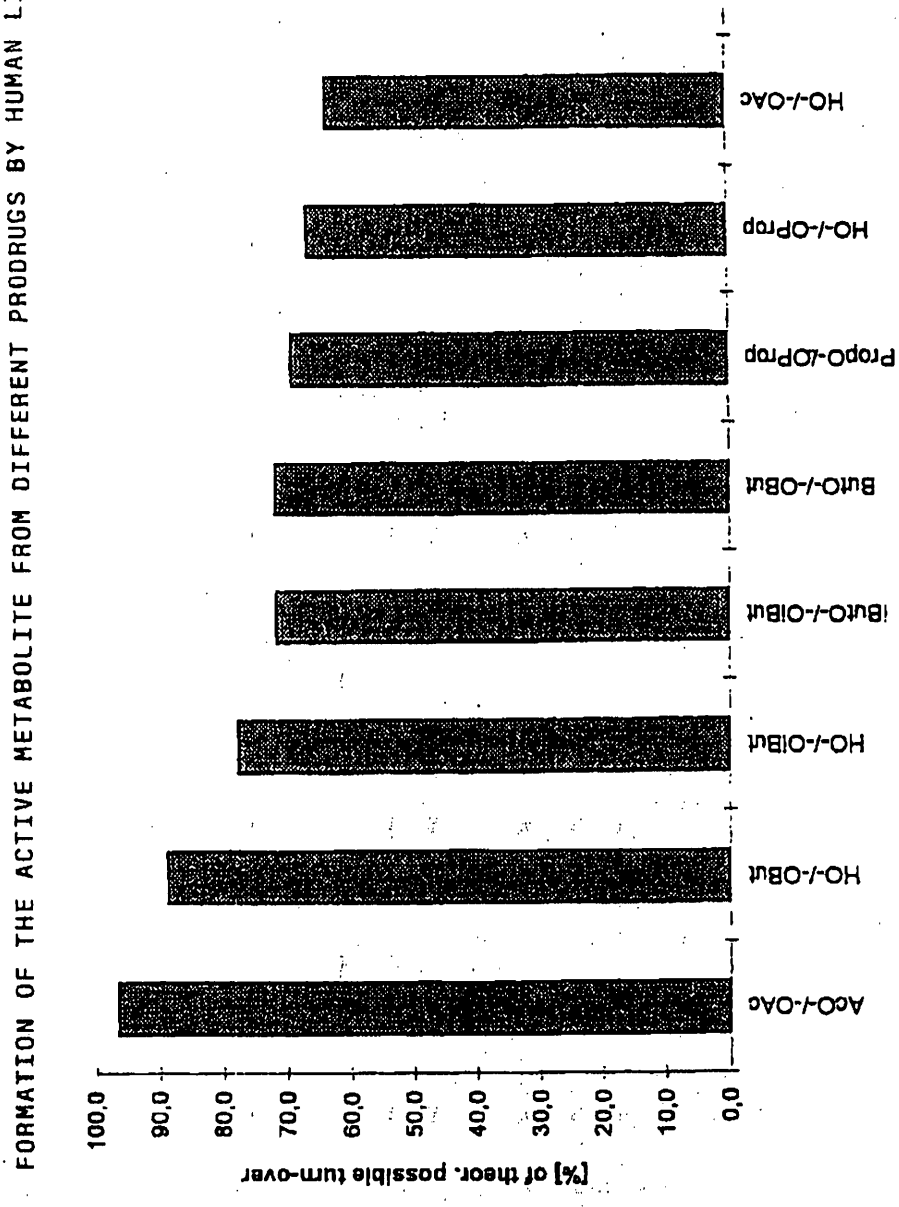
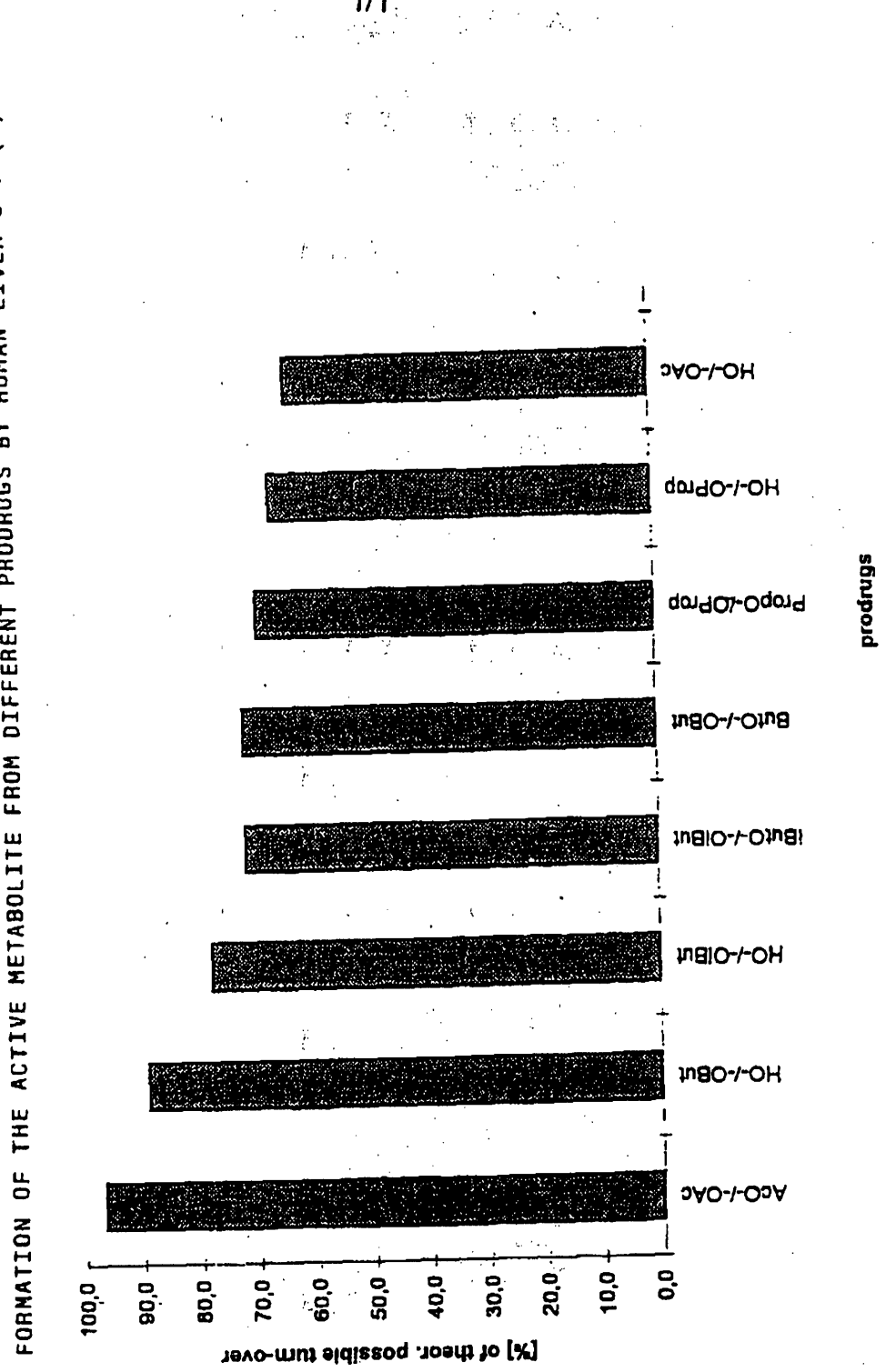

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h
[%] of theor. possible turn-over
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
AcO-/-OAc
HO-/-OBut
HO-/-OIBut
BuO-/-OBut
PropO-/OProp
HO-/-OProp
HO-/-OAc
prodrugs

FIG. 1


FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h
[%] of theor. possible turn-over
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
AcO-/-OAc
HO-/-OBut
HO-/-OIBut
HO-/-OAc
HO-/-OProp
PropO-/OProp
ButO-/-OBut
IButO-/-OIBut
prodrugs

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(PCT Rule 61.2)

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Date of mailing: 18 November 1999 (18.11.99)	
International application No.: PCT/EP99/03212	Applicant's or agent's file reference: 10022/um
International filing date: 11 May 1999 (11.05.99)	Priority date: 12 May 1998 (12.05.98)
Applicant: MEESE, Claus et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

24 June 1999 (24.06.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: J. Zahra
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

2946835

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Albrecht, Thomas
KRAUS & WEISERT
Thomas-Wimmer-Ring 15
80539 München
ALLEMAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	26.07.00
Applicant's or agent's file reference 10022/um	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/03212	11/05/1999	12/05/1998

Applicant
SCHWARZ PHARMA AG.et.al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel.+49 89 2399-8031

Form PCT/IPEA/416 (July 1992) SR22429, 21.07.2000

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: ASSISTANT COMMISSIONER FOR PATENTS
Box PCT
Washington, D.C. 20231

U.S. APPLICATION NO		FIRST NAMED APPLICANT	ATTY. DOCKET NO
09/700094		MEESE C	MBHB00-1121

MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, IL 60606

INTERNATIONAL APPLICATION NO.
PCT/EP99/03212

I.A. FILING DATE	PRIORITY DATE
11 MAY 99	12 MAY 98

DATE MAILED: 05 DEC 2000

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

1. The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as
   - ☐ a Designated Office (37 CFR 1.494),
   - ☒ an Elected Office (37 CFR 1.495):

   ☒ U.S. Basic National Fee.
   ☒ Copy of the international application in:
   - ☐ a non-English language.
   - ☒ English.

   ☒ Translation of the international application into English.
   ☒ Oath or Declaration of inventors(s) for DO/EO/US.
   ☐ Copy of Article 19 amendments.
   ☐ Translation of Article 19 amendments into English.
   ☐ The International Preliminary Examination Report in English and its Annexes, if any.
   ☐ Translation of Annexes to the International Preliminary Examination Report into English.
   ☒ Preliminary amendment(s) filed 8 nov 2000 and _____.
   ☒ Information Disclosure Statement(s) filed 8 nov 2000 and _____.
   ☐ Assignment document.
   ☐ Power of Attorney and/or Change of Address.
   ☐ Substitute specification filed _____.
   ☐ Verified Statement Claiming Small Entity Status.
   ☒ Priority Document.
   ☒ Copy of the International Search Report ☒ and copies of the references cited therein.
   ☐ Other:

2. The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:
   - ☐ a. Translation of the application into English. Note a processing fee will be required if submitted later than the appropriate 20 or 30 months from the priority date.
     - ☐ The current translation is defective for the reasons indicated on the attached Notice of Defective Translation.
   - ☐ b. Processing fee for providing the translation of the application and/or the Annexes later than the appropriate 20 or 30 months from the priority date (37 CFR 1.492(f)).
   - ☒ c. Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date.
     - ☐ The current oath or declaration does not comply with 37 CFR 1.497(a) and (b) for the reasons indicated on the attached PCT/DO/EO/917.
   - ☒ d. Surcharge for providing the oath or declaration later than the appropriate 20 or 30 months from the priority date (37 CFR 1.492(e)).

3. Additional claim fees of $_____ as a ☐ large entity ☐ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due. See attached PTO-875.

ALL OF THE ITEMS SET FORTH IN 2(a)-2(d) AND 3 ABOVE MUST BE SUBMITTED WITHIN ONE MONTH FROM THE DATE OF THIS NOTICE OR BY ☐ 21 OR ☐ 31 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

4. Translation of the Annexes MUST be submitted no later that the time period set above or the annexes will be cancelled. Note processing fee will be required if submitted later than 30 months from the priority date.

5. ☐ The Article 19 amendments are cancelled since a translation was not provided by the appropriate 20 (37 CFR. 494(d)) or 30 (37 CFR 1.495(d)) months from the priority date.

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

A copy of this notice MUST be returned with this response.

Enclosed:
☐ PCT/DO/EO/917 ☐ Notice of Defective Translation
☐ PTO-875

FORM PCT/DO/EO/905 (December 1997)

SHELBY VIGIL, PARALEGAL
Telephone: 703-305-3653

JC09 Rec'd PCT/PTO 02 JAN 200.

#3

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 00,1121)

In application of:)
)
Meese and Sparf)
)
Serial No. 09/700,094)
) **Group Art Unit: TBA**
Filed: November 8, 2000)
)
For: Novel Derivatives of 3,3-Diphenylpropylamines)

TRANSMITTAL LETTER

BOX PCT
Asst. Commissioner for Patents
Washington, D.C. 20231

01/03/2001 IVUIIT 00000042 09700094
01 FC:154 130.00 OP

Dear Sir:

In regard to the above identified application,

1. We are transmitting herewith the attached:

   a) copy of Notice to File Missing Requirements;
   b) Response to Notice to File Missing Requirements;
   c) Declaration and Power of Attorney; and
   d) return receipt postcard.

2. With respect to fees:

   a) A check in the amount of $130.00 is enclosed.
   b) Please charge any underpayment or credit any overpayment our Deposit Account, No. 13-2490.

3. CERTIFICATE OF MAILING UNDER 37 CFR § 1.8: The undersigned hereby certifies that this Transmittal Letter and the paper, as described in paragraph 1, are being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Asst. Commissioner for Patents, Washington, D.C. 20231 on December 27, 2000.

Respectfully submitted,

Date: December 27, 2000

Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive
Chicago, IL 60606
(312)913-0001

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: ASSISTANT COMMISSIONER FOR PATENTS
Box PCT
Washington, D.C. 20231

U.S. APPLICATION NO.		FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/700094		MEESE C	MBHB00-1121

MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
CHICAGO, IL 60606

INTERNATIONAL APPLICATION NO.
PCT/EP99/03212

I.A. FILING DATE	PRIORITY DATE
11 MAY 99	12 MAY 98

DATE MAILED: 04 DEC 2000

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

1. The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as
   - ☐ a Designated Office (37 CFR 1.494),
   - ☒ an Elected Office (37 CFR 1.495):

DOCKETED
DEC 18 2000
DUE DATE: 1-5-01
BY: MZ AB

- ☒ U.S. Basic National Fee.
- ☒ Copy of the international application in:
  - ☐ a non-English language.
  - ☒ English.
- ☒ Translation of the international application into English.
- ☒ Oath or Declaration of inventor(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments.
- ☐ Translation of Article 19 amendments into English.
- ☐ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Translation of Annexes to the International Preliminary Examination Report into English.
- ☒ Preliminary amendment(s) filed 8 nov 2000 and _____.
- ☒ Information Disclosure Statement(s) filed 8 nov 2000 and _____.
- ☐ Assignment document.
- ☐ Power of Attorney and/or Change of Address.
- ☐ Substitute specification filed _____.
- ☐ Verified Statement Claiming Small Entity Status.
- ☒ Priority Document.
- ☒ Copy of the International Search Report ☒ and copies of the references cited therein.
- ☐ Other:

2. The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:
   - ☐ a. Translation of the application into English. Note a processing fee will be required if submitted later than the appropriate 20 or 30 months from the priority date.
     - ☐ The current translation is defective for the reasons indicated on the attached Notice of Defective Translation.
   - ☐ b. Processing fee for providing the translation of the application and/or the Annexes later than the appropriate 20 or 30 months from the priority date (37 CFR 1.492(f)).
   - ☒ c. Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date.
     - ☐ The current oath or declaration does not comply with 37 CFR 1.497(a) and (b) for the reasons indicated on the attached PCT/DO/EO/917.
   - ☒ d. Surcharge for providing the oath or declaration later than the appropriate 20 or 30 months from the priority date (37 CFR 1.492(e)).

3. Additional claim fees of $_____ as a ☐ large entity ☐ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due. See attached PTO-875.

ALL OF THE ITEMS SET FORTH IN 2(a)-2(d) AND 3 ABOVE MUST BE SUBMITTED WITHIN ONE MONTH FROM THE DATE OF THIS NOTICE OR BY ☐ 21 OR ☐ 31 MONTHS FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

4. Translation of the Annexes MUST be submitted no later that the time period set above or the annexes will be cancelled. Note processing fee will be required if submitted later than 30 months from the priority date.
5. ☐ The Article 19 amendments are cancelled since a translation was not provided by the appropriate 20 (37 CFR. 494(d)) or 30 (37 CFR 1.495(d)) months from the priority date.

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

A copy of this notice MUST be returned with this response.

Enclosed:
☐ PCT/DO/EO/917 ☐ Notice of Defective Translation
☐ PTO-875

FORM PCT/DO/EO/905 (December 1997)

SHELBY VIGIL, PARALEGAL
Telephone: 703-305-3653

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 00,1121)

In application of:	)
Meese and Sparf	)
Serial No. 09/700,094	)
	) **Group Art Unit: TBA**
Filed: November 8, 2000	)
For: Novel Derivatives of 3,3-Diphenylpropylamines	)

RESPONSE TO NOTICE OF MISSING REQUIREMENTS

BOX PCT
Asst. Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Notice of Missing parts, applicants submit herewith an executed combined Declaration and Power of Attorney. In accordance with the surcharge requirement of 37 CFR 1.492(e), also enclosed is a check in the amount of $130.00.

Respectfully submitted,

Date: December 27, 2000

Michael S. Greenfield
Registration No. 37,142

McDonnell Boehnen Hulbert & Berghoff
300 South Wacker Drive, 32nd Floor
Chicago, IL 60606

Telephone: 312-913-0001
Facsimile: 312-913-0002

CERTIFICATE OF MAILING (37 C.F.R. 1.8a)
I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington D.C. 20231, on December 27, 2000.

Date: December 27, 2000

Michael S. Greenfield

Case No.: MBHB00,1121

DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Novel Derivatives of 3,3-diphenylpropylimines

the specification of which is attached hereto unless the following space is checked:

☒ was filed on November 8, 2000 as United States Application Serial Number _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s):

	Number	Country	Day/Month/Year Filed
1.	98108608.5	EPO	12 May 1998
2.			

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

	Application Number	Filing Date
1.		
2.		

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

	Application Number	Filing Date	Status: patented, pending, abandoned
1.	PCT/EP99/03212	11 May 1999	Abandoned

WELL BOEHNEN
T & BERGHORN
...TH WACKER DRIVE
O ILLINOIS 60606
ONE (312) 913-0001

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and I direct that all correspondence be addressed to that Customer Number.

Customer Number: 020306
Principal attorney or agent: Michael S. Greenfield, Reg. No. 37,142
Telephone number: 312-913-0001

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first inventor: Claus Moese

Inventor's signature: [signature] Date: 8 December 2000
Residence: Germany
Citizenship: Germany
Post Office Address: Kreuzberger Strasse 50, D-40789 ~~Monheim~~ DM

Full name of second joint inventor: Bengt Sparf

Inventor's signature: [signature] Date: 13 December 2000
Residence: Sweden
Citizenship: Sweden
Post Office Address: Drottningsvägen 6, S-142 65 Trångsund SE

DONNELL BOEHMEN
[illegible]
[illegible] WACKER DRIVE
CAGO, ILLINOIS 60604
PHONE (312) 913-0001

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: ASSISTANT COMMISSIONER FOR PATENTS
Washington, D C. 20231

US APPLICATION NO	FIRST NAMED APPLICANT	ATTY DOCKET NO.
09/700094	MEESE C	MBHB00-1121

INTERNATIONAL APPLICATION NO
PCT/EP99/03212

1 A FILING DATE	PRIORITY DATE
11 MAY 99	12 MAY 98

MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
SUITE 3200
CHICAGO, IL 60006

DATE MAILED 16 JAN 2001

NOTIFICATION OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

1. The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as ☐ a Designated Office (37 CFR 1.494), ☒ an Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is **ACCEPTED** for national patentability examination in the United States Patent and Trademark Office.

2. The United States Application Number assigned to the application is shown above and the relevant dates are:

2 jan 2001	2 jan 2001
35 U.S.C. 102(e) DATE	DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371(C) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

3. ☒ A request for immediate examination under 35 U.S.C. 371(f) was received on 8 nov 2000 and the application will be examined in turn.

4. The following items have been received:
- ☒ U.S. Basic National Fee.
- ☒ Copy of the international application in:
  - ☒ a non-English language.
  - ☐ English.
- ☒ Translation of the international application into English.
- ☒ Oath or Declaration of inventors(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments. ☐ Translation of Article 19 amendments into English.
  The Article 19 amendments ☐ have ☐ have not been entered.
- ☒ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Copy of the Annexes to the International Preliminary Examination Report (IPER).
  - ☐ Translation of Annexes to the IPER into English.
  The Annexes ☐ have ☐ have not been entered.
- ☒ Preliminary amendment(s) filed 8 nov 2000 and _____.
- ☒ Information Disclosure Statement(s) filed 8 nov 2000 and _____.
- ☐ Assignment document.
- ☐ Power of Attorney and/or Change of Address.
- ☐ Substitute specification filed _____.
- ☐ Verified Statement Claiming Small Entity Status.
- ☒ Priority Document.
- ☒ Copy of the International Search Report ☒ and copies of the references cited therein.
- ☐ Other:

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

Shelby J. Vigil

FORM PCT/DO/EO/903 (December 1997)

Telephone: 703-305-3653

#1 6-27-01

Practitioner's Docket No. 55647 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

☒ In re application of: Meese et al.

Serial No.: 09/700,094 Group No.: 1614
Filed: January 2, 2001 Examiner: Not Yet Assigned
For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

☐ Patent No*: Issued:

*NOTE: *Insert name(s) of inventor(s) and title also for patent.*

Assistant Commissioner for Patents
Washington, D.C. 20231

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST (REVOCATION OF PRIOR POWERS)

As assignee of record of the entire interest of the above identified

☒ application,

☐ patent,

REVOCATION OF PRIOR POWERS OF ATTORNEY

all powers of attorney previously given are hereby revoked and

NEW POWER OF ATTORNEY

the following attorney(s) and/or agent(s) are hereby appointed to prosecute and transact all business in the Patent and Trademark Office connected therewith.

David G. Conlin	Reg. No. 27,026	Christine C. O'Day	Reg. No. 38,256
George W. Neuner	Reg. No. 26,964	Robert L. Buchanan	Reg. No. 40,927
Linda M. Buckley	Reg. No. 31,003	David E. Tucker	Reg. No. 27,840
Peter J. Manus	Reg. No. 26,766	Lisa Swiszcz Hazzard	Reg. No. 44,368
Peter F. Corless	Reg. No. 33,860	George W. Hartnell	Reg. No. 42,639
Cara Z. Lowen	Reg. No. 38,227	Kathleen Carr	Reg. No. 41,658
William J. Daley, Jr.	Reg. No. 35,487	Stewart L. Gitler	Reg. No. 31,256

(check the following item; if applicable)

☐ Attached, as part of this power of attorney, is the authorization of the above-named attorney(s) to accept and follow instructions from my representative(s).

SEND CORRESPONDENCE TO: **DIRECT TELEPHONE CALLS TO:**

Peter F. Corless
EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman, IP Group
130 Water Street
Boston, MA 02109

Peter F. Corless: (617) 523-3400

Customer No.:

Schwarz Pharma AG
(type or print identity of assignee of entire interest)

Alfred-Nobel-Straße 10
Address
Monheim, Germany D-40789

☐ Recorded in PTO on _____
Reel _____
Frame _____

*The executed Assignment document was forwarded to the U.S. Patent Office on January 9, 2001 (copy enclosed). Applicant has not yet received the Notice of Recordation.

ASSIGNEE STATEMENT

Attached to this power is a "STATEMENT UNDER 37 C.F.R. 3.73(b)."

Signature

Date March 01, 2001

ppa. Klaus-Dieter Hommerich i.V. Dietrich W. Schacht
(type or print name of person authorized to sign on behalf of assignee)

Authorized Officer Assistant Manager
Title

NOTE: The assignee of the entire interest may revoke previous powers and be represented by an attorney of his or her selection. 37 C.F.R. § 1.36.

(check the following item, if it forms a part of this power of attorney)

☐ Added page—Authorization of attorney(s) to accept and follow instructions from representative.

GAU 1614

Practitioner's Docket No. 55647 (00.1121) **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Meese et al.
Application No.: 09/700,094 Group No.: 1614
Filed: January 2, 2001
For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES Examiner: Not Yet Assigned
Patent*: Issue Date:
Reexamination No.: Issue Date:
Reissue: Issue Date:

*NOTE: *Insert name(s) of inventor(s) and title for patent.*

Assistant Commissioner for Patents
Washington, D.C. 20231

STATEMENT UNDER 37 C.F.R. § 3.73(b)— ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*
(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

☒ deposited with the United States Postal Service in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

37 C.F.R. § 1.8(a)

☒ with sufficient postage as first class mail.

37 C.F.R. § 1.10*

☐ as "Express Mail Post Office to Addressee" Mailing Label No. _____ ***(mandatory)***

TRANSMISSION

☐ transmitted by facsimile to the Patent and Trademark Office.

Date: 4/20/01

Signature

LAURA M. McGUIRE

(type or print name of person certifying)

***WARNING:** Each paper or fee filed by Express Mail must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

NOTE: 37 CFR 3.73(b) states: "When an assignee seeks to take action in a matter before the Office with respect to a patent application, . . ., patent, registration, or reexamination proceeding, the assignee must establish its ownership of the property to the satisfaction of the Commissioner. Ownership is established by submitting to the Office, in the Office file related to the matter in which action is sought to be taken, documentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed assignment submitted for recording) or by specifying (e.g., reel and frame number) where such evidence is recorded in the Office. The submission establishing ownership must be signed by a party authorized to act on behalf of the assignee. Documents submitted to establish ownership may be required to be recorded as a condition to permitting the assignee to take action in a matter pending before the Office."

NOTE: "Section 3.73(b) is amended to remove the sentence requiring an assignee to specifically state that the evidentiary documents have been reviewed and to certify that title is in the assignee seeking to take action. The sentence is deemed to be unnecessary in view of the amendment to §§ 1.4(d) and 10.18." Notice of Oct. 10, 1997, 62 Fed. Reg. 53,131, at 53,174.

1. The assignee(s) of the entire right, title and interest hereby seek(s) to take action in the PTO in this matter.

IDENTIFICATION OF ASSIGNEE

2. Schwarz Pharma AG
Name of assignee

Corporation
Type of assignee, e.g., corporation, partnership, university, government agency, etc.

PERSON AUTHORIZED TO SIGN

3. ppa. Klaus-Dieter Hommerich i.V. Dietrich W. Schacht
(type name of person authorized to sign on behalf of assignee)

Authorized Officer Assistant Manager
Title of person authorized to sign

NOTE: The Notice of April 30, 1993 (1150 O.G. 62-64) points out:

"The statement under 37 CFR 3.73(b) may be signed on behalf of the assignee in the following two manners if the assignee is an organization (e.g., corporation, partnership, university, government agency, etc.).

"(1) The statement may be signed by a person in the organization having apparent authority to sign on behalf of the organization. An officer (president, vice-president, secretary, or treasurer) is presumed to have authority to sign on behalf of the organization. The signature of the chairman of the board of directors is acceptable, but not the signature of an individual director. A person having a title (manager, director, administrator, general counsel) that does not clearly set forth that person as an officer of the assignee is not presumed to be an officer of the assignee or to have authority to sign the statement on behalf of the assignee. A power of attorney from the inventors in an organization to a practitioner to prosecute a patent application does not make the practitioner an official of an assignee or empower the practitioner to sign the statement on behalf of the assignee.

"(2) The statement may be signed by any person, if the statement includes an averment that the person is empowered to sign the statement on behalf of the assignee and, if not signed by a registered practitioner, the statement must be in oath or declaration form. Where a statement does not include such an averment, and the person signing does not hold a position in the organization that would give rise to a presumption that the person is empowered to sign the statement on behalf of the assignee, evidence of the person's authority to sign will be required."

[Author's Note: The requirement for an oath or declaration for this statement by a person not a registered practitioner was rescinded by the rules effective December 1, 1997.]

(complete the following, if applicable)

☒ I, the person signing below, state that I am empowered to sign this statement on behalf of the assignee.

BASIS OF ASSIGNEE'S INTEREST

Ownership by the assignee is established as follows:

A.

1. ☐ An assignment from the inventor(s) of the matter identified above, which was recorded in the PTO at

   Reel _____, Frame _____.

2. ☐ An assignment (document) separately being submitted for recordal herewith.

AND/OR

B. ☒ A chain of title from the inventor(s) to the current assignee as shown below:

1. From: Claus MEESE and Bengt SPARF
   Name of inventor(s)

   To: Schwarz Pharma AG

   Recorded in PTO: Reel _____, Frame ____

2. From: _____
   Name of inventor(s) or assignee

   To: _____

   Recorded in PTO: Reel _____, Frame ____

3. From: _____
   Name of inventor(s) or assignee

   To: _____

   Recorded in PTO: Reel _____, Frame ____

(check item below, and add details, if applicable)

☐ Additional documents in the chain of title are listed in the attached Supplemental Sheet.

COPIES OF DOCUMENTS IN CHAIN OF TITLE

(complete this item, if copies are being sent)

☒ Copies of the assignment(s) or other document(s) in the chain of title are attached as follows:

☐ A ☐ 1 ☐ 2

☒ B ☒ 1 ☐ 2 ☐ 3

(Signature of authorized person)

ppa. Klaus-Dieter Hommerich i.V. Dietrich W. Schacht

(type or print name of authorized person)

Authorized Officer Assistant Manager

Title of authorized person

SIGNATURE OF PRACTITIONER

Reg. No.: 33,860

Peter F. Corless

(type or print name of practitioner)

Tel. No.: (617)523-3400

EDWARDS & ANGELL, LLP

P.O. Address

Customer No.:

P.O. BOX 9169

Boston, Massachusetts 02209

H 8

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
09/700,094	01/02/2001	Claus Meese	MBHB00-1121

CONFIRMATION NO. 1408

OC000000006234276

OC000000006234276

PETER F. CORLESS
EDWARDS & ANGELL, LLP
130 WATER STREET
BOSTON, MA 02109

Date Mailed: 06/27/2001

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/24/2001.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Customer Service Center
Initial Patent Examination Division (703) 308-1202

OFFICE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO./TITLE
09/700,094	01/02/2001	Claus Meese	MBHB00-1121

CONFIRMATION NO. 1408

20306
MCDONNELL BOEHNEN HULBERT & BERGHOFF
300 SOUTH WACKER DRIVE
SUITE 3200
CHICAGO, IL 60606

OC0000000006234189

Date Mailed: 06/27/2001

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/24/2001.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Customer Service Center
Initial Patent Examination Division (703) 308-1202

OFFICE COPY

Docket No. 55647 (4107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: C. Meese et al.

Serial No.: 09/700,094 GROUP: 1614

Filed: January 2, 2001 EXAMINER: Not Yet Assigned

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Assistant Commissioner for Patents
Washington, D.C. 20231

****

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Date 8-13-01 By: Christine C. O'Day
Christine C. O'Day

****

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§1.56 and 1.97, Applicants herewith submit the publications and/or patents shown on the attached form PTO-1449, for consideration by the Examiner in connection with the examination of the above-identified patent application.

REMARKS

In accordance with the provisions of 37 C.F.R. §1.97, this statement is being filed:

__X__ (1) within three (3) months of the Filing Date or **before the mailing date of the First Office Action** on the merits; or

_____ (2) within three months of the mailing date of the Written Opposition issued by the: _____Patent Office (dated _____); or

___ (3) after the period defined in (1) but before the mailing date of a Final Rejection or Notice of Allowance, and the requisite

Certification or fee under Rule 1.17(p), namely $240.00, is included herein; or

___ (4) after the mailing date of a Final Rejection or Notice of Allowance but before the payment of the Issue Fee, and the requisite Certification, petition, and petition fee are included herein.

It is respectfully requested that each of the documents shown on the attached form(s) PTO-1449 be made of record in this application. Copies of these documents (CHECK ONE):

_X_ are enclosed herewith; or

___ have been cited in the parent application, and are thus not being resubmitted herein.

Early examination and allowance of the present application are respectfully solicited.

FEE AUTHORIZATION

Should any fees associated with the submission be required, the Commissioner is authorized to charge the missing fee to our Deposit Account, No. 04-1105. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,

Christine C. O'Day (Reg. 38,256)
DIKE, BRONSTEIN, ROBERTS & CUSHMAN
Intellectual Property Practice Group
Edwards & Angell, LLP
PO Box 9169
Boston, MA 02209
(617) 439-4444

Date: August 13, 2001

FORM PTO-1449	DOCKET NO.: 55647	SERIAL NO.: 09/700,094
INFORMATION DISCLOSURE STATEMENT	APPLICANT(S): C. Meese et al.	
	FILING DATE: January 2, 2001	GROUP NO.: ~~4644~~ 1622

UNITED STATES PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES/NO
2T	AA	WO 89/06644	7/27/89	WIPO	—	—	—
2T	AB	WO 94/11337	5/26/94	WIPO	—	—	—

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

2T	AC	Nilvebrant et al., *European Journal of Pharmacology*, 327(1997) pp. 195-207.

Examiner:	Date:
	28 JANUARY 2003

UNITED STATE DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
			HA

EXAMINER	
ART UNIT	PAPER NUMBER
	10

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev 11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/700,094	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1623	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-24 and 28-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-16, 18-24, and 28-38* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Lack of Unity of Invention

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group 1, claim 1 in part (wherein R and R' are b), 2-10, and 16, 18, 19 and 20, drawn to ester derivatives of the diphenylpropylamine compound of formula I and processes for the preparation thereof.

Group 2, claim 1 in part (wherein R and R' are a or g), 2, 11, 12, and 21-23, drawn to ethers and silyl ether derivatives of the diphenylpropylamine compound of formula I and processes for the preparation thereof.

Group 3, claim 1 in part (wherein R and R' are c and d), 2, 13, 14 and 24 and 33, drawn to carbonate and carbamate derivatives of the diphenylpropylamine compound of formula I and processes for the preparation thereof.

Group 4, claim 1 in part, (wherein R and R' are e), and 2, drawn to sulfamate derivatives of the diphenylpropylamine compound of formula I.

Group 5, claim 1 in part, (wherein R and R' are f), and 2, drawn to inorganic ester derivatives of the diphenylpropylamine compound of formula I.

Group 6, claim 15, drawn to (i) cyclic diesters of formulae IX and IX', (ii) a benzoic acid ester of the diphenylpropylamine compound of formula I, (iii) poly-co-DL-lactides of the diphenylpropylamine compound of formula I and (iv) a 1β-D-glucuronosyloxymethyl derivative of the diphenylpropylamine compound of formula I.

Group 7, claim 28 in part (wherein R is a or g) and 29, drawn to ether and silyl ether derivatives of the compound of formula VII'.

Group 8, claim 28 in part (wherein R is b), 29, 30, and 32, drawn to ester derivatives of the compound of formula VII' and a process for preparing the phenolic monoester derivative.

Group 9, claim 28 in part (wherein R is c or d), 29, 31 and 33, drawn to carbonate and carbamate derivatives of the compound of formula VII' and a process for the preparation thereof.

Group 10, claim 28 in part (wherein R is e or f), and 29, drawn to sulfamate and inorganic ester derivatives of the compound of formula VII'.

The composition and method of use claims will be examined along with the elected inventions and commensurate in scope therewith if dependent thereupon.

The special technical feature in common to groups 1-10 is a structural moiety which was known in the art at the time the inventions were made (WO 94/11337 see first page), and as such does not represent a contribution over the prior art, therefore groups 1-10 represent different inventions pursuant to 37 CFR 1.475 (a).

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (703) 305-2050 and facsimile telephone number is (703) 746-3176. The examiner can normally be reached Monday-Friday from 8:00am to 4:00pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Geist, can be reached at (703) 308-1701. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

GARY GEIST
SUPERVISORY PATENT EXAMINER
TECH CENTER 1600

Notice of References Cited	Application/Control No. 09/700,094	Applicant(s)/Patent Under Reexamination MEESE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification	
	A	US-				
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification	
*	N	WO 94/11337	05-1994	PCT	Johansson et al (DUPLICATE CITATION)		--
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707 05(a).)
Dates in MM YYYY format are publication dates Classifications may be US or foreign.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C 20231
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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

7590 04/10/2002

PETER F. CORLESS
EDWARDS & ANGELL, LLP
130 WATER STREET
BOSTON, MA 02109

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	11

DATE MAILED: 04/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

Notice of Abandonment	Application No.	Applicant(s)	
	09/700,094	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

This application is abandoned in view of:

1. ☒ Applicant's failure to timely file a proper reply to the Office letter mailed on *07 September 2001*.
   (a) ☐ A reply was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply (including a total extension of time of _____ month(s)) which expired on _____.
   (b) ☐ A proposed reply was received on _____, but it does not constitute a proper reply under 37 CFR 1.113 (a) to the final rejection.
   (A proper reply under 37 CFR 1.113 to a final rejection consists only of: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114).
   (c) ☐ A reply was received on _____ but it does not constitute a proper reply, or a bona fide attempt at a proper reply, to the non-final rejection. See 37 CFR 1.85(a) and 1.111. (See explanation in box 7 below).
   (d) ☒ No reply has been received.

2. ☐ Applicant's failure to timely pay the required issue fee and publication fee, if applicable, within the statutory period of three months from the mailing date of the Notice of Allowance (PTOL-85).
   (a) ☐ The issue fee and publication fee, if applicable, was received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the statutory period for payment of the issue fee (and publication fee) set in the Notice of Allowance (PTOL-85).
   (b) ☐ The submitted fee of $_____ is insufficient. A balance of $_____ is due.
   The issue fee required by 37 CFR 1.18 is $_____. The publication fee, if required by 37 CFR 1.18(d), is $_____.
   (c) ☐ The issue fee and publication fee, if applicable, has not been received.

3. ☐ Applicant's failure to timely file corrected drawings as required by, and within the three-month period set in, the Notice of Allowability (PTO-37).
   (a) ☐ Proposed corrected drawings were received on _____ (with a Certificate of Mailing or Transmission dated _____), which is after the expiration of the period for reply.
   (b) ☐ No corrected drawings have been received.

4. ☐ The letter of express abandonment which is signed by the attorney or agent of record, the assignee of the entire interest, or all of the applicants.

5. ☐ The letter of express abandonment which is signed by an attorney or agent (acting in a representative capacity under 37 CFR 1.34(a)) upon the filing of a continuing application.

6. ☐ The decision by the Board of Patent Appeals and Interference rendered on _____ and because the period for seeking court review of the decision has expired and there are no allowed claims.

7. ☐ The reason(s) below:

PAUL J. KILLOS
PRIMARY EXAMINER
AU 1623

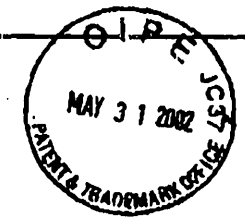
Petitions to revive under 37 CFR 1.137(a) or (b), or requests to withdraw the holding of abandonment under 37 CFR 1.181, should be promptly filed to minimize any negative effects on patent term.

9200/16

CERTIFICATE OF MAILING BY FIRST CLASS MAIL (37 CFR 1.8) Applicant(s): C. Meese et al.			Docket No. 55647 (45107)
Serial No. 09/700,094	Filing Date January 2, 2001	Examiner Z. Tucker	Group Art Unit 1624

Invention: **Novel Derivatives of 3,3-Diphenylpropylamines**

#12



I hereby certify that this **Petition to Withdraw a Holding of Abandonment Pursuant to 37 CFR 1.181**
(Identify type of correspondence)

is being deposited with the United States Postal Service as first class mail in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on **May 21, 2002**
(Date)

Susan M. Dillon
(Typed or Printed Name of Person Mailing Correspondence)

Susan M Dillon
(Signature of Person Mailing Correspondence)

Note: Each paper must have its own certificate of mailing.

P07A/REV03

Docket No. 55647 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	C. Meese et al.		
SERIAL NO.:	09/700,094	GROUP:	1624
FILED:	January 2, 2001	EXAMINER:	Z. Tucker
FOR:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

PETITION TO WITHDRAW A HOLDING OF ABANDONMENT
PURSUANT TO 37 C.F.R. §1.181

Pursuant to 37 C.F.R. §1.181, Applicants respectfully petition for withdrawal of the holding of abandonment for the above-referenced patent application, which, as indicated in a Notice of Abandonment mailed by the Patent Office on April 10, 2002, was deemed to be abandoned for Applicants' alleged failure to properly respond to an Office letter mailed on September 7, 2001.

STATEMENT OF FACTS

The Attorneys of Record for Applicants confirm receipt of the Office letter of September 7, 2001, which Office letter indicated that claims 1-16, 18-24, and 28-38 were subject to a Restriction Requirement.

On November 29, 2001, the Attorneys of Record for Applicants sent via first-class mail, a complete and timely response to the Office letter of September 7, 2001. In particular, Applicants sent a response to the Assistant Commissioner for Patents, Washington, D.C. 20231, which contained the following materials, copies of which are enclosed herein:

(1) An amendment transmittal including (i) a duly executed certificate of mailing bearing the date of November 29, 2001, and (ii) a petition for a two-month extension of time;

(2) An amendment and response to the Restriction Requirement;

(3) A copy of the International Preliminary Examination Report for the corresponding international application, provided in support of a traverse to the Restriction Requirement;

(4) A check for $400.00 representing the extension fee; and

(5) A return receipt postcard.

As indicated in (1) above, the amendment transmittal included a duly executed certificate of mailing (pursuant to 37 C.F.R. §1.8). The certificate of mailing properly certified that the correspondence was deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C., on November 29, 2001.

The Attorneys of Record for the subject application received a Notice of Abandonment (mail date: April 10, 2002) for the above-referenced application on April 17, 2002, for Applicants' alleged failure to submit a proper response to the Office letter of September 7, 2001.

RELIEF REQUESTED

Applicants respectfully request that the Commissioner, based on the following arguments, withdraw the erroneous holding of abandonment and enter the enclosed response into the record for the subject application.

ARGUMENT

The within petition and the related enclosures are being filed within two (2) months of the mail date of the Notice of Abandonment. Accordingly, the within petition is considered to be timely filed [37 C.F.R. 1.181(f)].

MPEP 711.04(c) provides that a petition to withdraw the holding of abandonment may be adequate relief when a response with a certificate of mailing has been filed by an applicant but was not received. The MPEP also suggests that a Petition to revive is not required in these

circumstances. The foregoing is believed to be applicable to the facts relating to the abandonment of the subject application.

In the instant case, Applicants filed a timely and complete response to the Office letter mailed on September 7, 2001, as evidenced by the enclosed materials. Thus, the abandonment of the subject application is wholly unintentional and erroneous.

CONCLUSION

In view of the foregoing, Applicants submit that the holding of abandonment be withdrawn. As evidenced by the enclosed materials, Applicants provided a timely and complete reply to the Office letter of September 7, 2001.

Accordingly, Applicants respectfully request withdrawal of the holding of abandonment of the above-referenced patent application, and entry of the enclosed response to the Office letter of September 7, 2001.

No fee is believed to be due in connection with the filing or consideration of this petition. In the event any fee(s) is/are due, however, please charge such fee(s) to Deposit Account No. 04-1105.

Respectfully submitted,

Date: 5-21-02 By: Christine C. O'Day

Christine C. O'Day (Reg. No. 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. No. (617) 439-4444

BOS2_301878.1

Practitioner's Docket No. 55647 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: C. Meese et al.

Serial No.: 09/700,094 Group No.: 1623

Filed: January 2, 2001 Examiner: Z. Tucker

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Assistant Commissioner for Patents
Washington, D.C. 20231

AMENDMENT TRANSMITTAL

1. Transmitted herewith is an amendment for this application.

STATUS

2. Applicant is
   - [ ] a small entity. A statement:
     - [ ] is attached.
     - [ ] was already filed.
   - [X] other than a small entity.

EXTENSION OF TERM

NOTE: "Extension of Time in Patent Cases (Supplement Amendments) — If a timely and complete response has been filed after a Non-Final Office Action, an extension of time is not required to permit filing and/or entry of an additional amendment after expiration of the shortened statutory period.

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

[X] deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: 11/29/01

FACSIMILE

☐ transmitted by facsimile to the Patent and Trademark Office.

Deanna Rivernider
Signature

Deanna M. Rivernider
(type or print name of person certifying)

If a timely response has been filed after a Final Office Action, an extension of time is required to permit filing and/or entry of a Notice of Appeal or filing and/or entry of an additional amendment after expiration of the shortened statutory period unless the timely-filed response placed the application in condition for allowance. Of course, if a Notice of Appeal has been filed within the shortened statutory period, the period has ceased to run." Notice of December 10, 1985 (1061 O.G. 34-35).

NOTE: See 37 C.F.R. 1.645 for extensions of time in interference proceedings, and 37 C.F.R. 1.550(c) for extensions of time in reexamination proceedings.

3. The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136 apply.

(complete (a) or (b), as applicable)

(a) [X] Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(4)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
[ ]	one month	$110.00	$55.00
[X]	two months	$400.00	$190.00
[ ]	three months	$870.00	$435.00
[ ]	four months	$1360.00	$680.00

Fee: $ 400.00

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured. The fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ 400.00

OR

(b) [ ] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. 1.16(b)-(d)) has been calculated as shown below:

	(Col.1) Claims Remaining After Amendment		(Col. 2) Highest No. Previously Paid For	(Col. 3) Present Extra	SMALL ENTITY Rate	SMALL ENTITY Addit. Fee	*OR*	OTHER THAN A SMALL ENTITY Rate	OTHER THAN A SMALL ENTITY Addit. Fee
Total	*	Minus	**	=	x $9 =	$		x $18 =	$
Indep.	*	Minus	***	= 0	x $39 =	$		x $78 =	$ 0
[ ] First Presentation of Multiple Dependent Claim					+ $130 =	$		+ $260 =	$ 0
					Total Addit. Fee	$_____	*OR*	Total Addit. Fee	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3,

** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest No. Previously Paid For" (Total or Indep.) is the highest number found in the appropriate box in Col. 1 of a prior amendment or the number of claims originally filed.

WARNING: *"After final rejection or action (§ 1.113) amendments may be made canceling claims or complying with any requirement of form which has been made." 37 C.F.R. 1.116(a) (emphasis added).*

(complete (c) or (d), as applicable)

(c) [X] No additional fee for claims is required.

OR

(d) [ ] Total additional fee for claims required $ _____.

FEE PAYMENT

5. [X] Attached is a check in the sum of $ 400.00 .
[ ] Charge Account No. _____ the sum of $ _____.
A duplicate of this transmittal is attached.

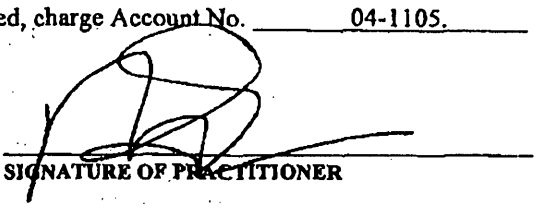
FEE DEFICIENCY

NOTE: *If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to charge the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, (1065 O.G. 31-33).*

6. [X] If any additional extension and/or fee is required, charge Account No. 04-1105.

AND/OR

[X] If any additional fee for claims is required, charge Account No. 04-1105.



SIGNATURE OF PRACTITIONER

Reg. No. 33,860

Peter F. Corless
(type or print name of practitioner)

Tel. No. (617) 523-3400

EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman, IP Group
P.O. Box 9169
P.O. Address
Boston, Massachusetts 02209

#12&B

Docket No. 55647

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese et al.

SERIAL NO.: 09/700,094 GROUP: 1623

FILED: January 2, 2001 EXAMINER: Z. Tucker

FOR: NOVEL DERIVATIES OF 3,3-DIPHENYLPROPYLAMINES

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Applicants are in receipt of the Office Action dated September 7, 2001. Please amend the above-identified application as follows.

IN THE CLAIMS

Please add the following new claim 39.

39. A pharmaceutical composition of claim 26 wherein the composition is a patch formulation.

REMARKS

Claim 39 has been added. No new matter has been added by virtue of that amendment. For instance, support for the new claim appears e.g. at page 36, lines 3-4 of the application.

Applicants respectfully request reconsideration of the Restriction Requirement.

A unity objection was not raised in the corresponding International Application (the present case was filed under 35 U.S.C. 371). A copy of the International Preliminary Examination Report is enclosed, which shows the application claims satisfied novelty and inventive step requirements.

Additionally, it is believed the searches of multiple Groups identified in the Restriction will be overlapping and, therefore, examination of multiple Groups would not cause undue burden. Indeed, significant expense and time would be required if divisional applications to each of the ten Groups identified in the Restriction must be separately prosecuted.

It is thus requested that all the presented subject matter be considered at this time. See, again, the International Preliminary Examination Report, copy enclosed. As an alternative, it is requested that at least Groups I through 5 be examined together at this time.

To be fully responsive to the Restriction, Applicants elect Group 1, as that Group is defined in the Office Action.

Respectfully, Applicants strongly disagree with statements on page 4 of the Office Action regarding what was known in the art. As discussed above, the International Preliminary Examination Report states the claims satisfy novelty and inventive step requirements.

Early consideration and allowance of the application are earnestly solicited.

Respectfully submitted,

Peter F. Corless (Reg. 33,860)
EDWARDS & ANGELL, LLP
Dike, Bronstein, Roberts & Cushman IP Group
P.O. Box 9169
Boston, MA 02209
(617) 523-3400

Mailing Date: November 29, 2001
Client: Kraus & Weisert (45107)
Inventors: C. Meese et al.
Serial No.: 09/700,094
Filing Date: January 2, 2001

Attorney/Sec: PFC/dmr
Docket No: 55647
Patent No
Grant Date

The dating stamp of the Patent and Trademark Office hereon will be taken as the date of filing of:

Amendment Transmittal; Response to Restriction Requirement; and check in the amount of $400.00.

Due Date: December 7, 2001

EDWARDS & ANGELL, LLP
COUNSELLORS AT LAW
since 1894
28 Lord Road Suite 230
Marlboro, MA 01752

EXPLANATION	AMOUNT
Code: 116	

57-1/115

1665

IT Four Hundred Dollars and 00/100 DOLLARS

TO THE ORDER OF	DESCRIPTION	CHECK NUMBER	CHECK AMOUNT
Hon. Comm for Patents,	(45107) 55647	1665	$ 400 00

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY
AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
WWW.USPTO.GOV

JAN 17 2003

#13

PETER F. CORLESS
EDWARDS & ANGELL, LLP
130 WATER STREET
BOSTON MA 02109

In re Application of :
Claus Meese et al :
Serial No.: 09/700,094 :PETITION DECISION
Filed: January 2, 2001 :
Attorney Docket No.: 55647(45107) :

This is in response to applicants' petition under 37 CFR 1.181, filed May 21, 2002 (duplicate filed November 19, 2002), requesting revival of the above-identified application based on a timely response to the last Office action. The delay in acting on this petition is regretted, however it was not forwarded for decision until recently.

A review of the file history indicates the examiner mailed an Office action to applicants on September 7, 2001, setting a one month shortened statutory period for reply. Upon failure to receive a reply, the application was held abandoned by Notice of Abandonment mailed April 10, 2002. Applicants states that a reply to the Office action was filed on November 29, 2001, accompanied by a request and fee for a two month extension of time. It appears that the reply was never received by the Office, possibly due to US Postal Service irregularities at the time. The copy of the reply which accompanied the petition has now been placed in the file in lieu of the original. In view applicants timely reply, the Notice of Abandonment was mailed in error and is withdrawn and the application is restored to a pending status with the mailing of this decision.

Applicant's petition is **GRANTED**.

The application will be forwarded to the examiner for further consideration.

Should there be any questions with respect to this decision, please contact William R. Dixon, Jr., by mail addressed to Director, Technology Center 1600, Washington, D.C. 20231, or by telephone at (703) 308-3824 or by facsimile transmission at (703) 305-7230.

Bruce M. Kisliuk
Director, Technology Center 1600

UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY
AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
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JAN 17 2002

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FEB 03 2003
TECH CENTER 1600/2900

PETER F. CORLESS
EDWARDS & ANGELL, LLP
130 WATER STREET
BOSTON MA 02109

In re Application of
Claus Meese et al
Serial No.: 09/700,094
Filed: January 2, 2001
Attorney Docket No.: 55647(45107)

:PETITION DECISION

RECEIVED
MAY 15 2003
TECH CENTER 1600/2900

This is in response to applicants' petition under 37 CFR 1.181, filed May 21, 2002 (duplicate filed November 19, 2002), requesting revival of the above-identified application based on a timely response to the last Office action. The delay in acting on this petition is regretted, however it was not forwarded for decision until recently.

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Should there be any questions with respect to this decision, please contact William R. Dixon, Jr., by mail addressed to Director, Technology Center 1600, Washington, D.C. 20231, or by telephone at (703) 308-3824 or by facsimile transmission at (703) 305-7230.

Bruce M. Kisliuk
Director, Technology Center 1600

#14

Docket No. 55647 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese et al.

SERIAL NO.: 09/700,094 GROUP: 1624

FILED: January 2, 2001 EXAMINER: Z. Tucker

FOR: NOVEL DERIVATIES OF 3,3-DIPHENYLPROPYLAMINES

Commissioner for Patents and Trademarks
Washington, D.C. 20231

SIR:

CHANGE OF ATTORNEY'S ADDRESS IN APPLICATION

NOTE: Section 601.03 (Change of Correspondence Address), M.P.E.P., 7th Edition states:

"Where an attorney or agent of record (or applicant, if he or she is prosecuting the application pro se) changes his or her correspondence address, he or she is responsible for promptly notifying the Patent and Trademark Office of the new correspondence address (including ZIP code number). The notification should also include his or her telephone number. A change of correspondence address may not be signed by an attorney or agent not of record (see MPEP Section 405).

"Unless the correspondence address is designated as the address associated with a Customer Number, a separate notification must be filed in each application for which a person is intended to receive communications from the Office. See MPEP Section 403 for Customer Number Practice. In those instances where a change in the correspondence address of a registered attorney or agent is necessary in a plurality of applications, the notification filed in each

---

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. Section 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

[ ] deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents and Trademarks, Washington, D.C. 20231.

Date: 1-28-03

FACSIMILE

[X] transmitted by facsimile to the Patent and Trademark Office (703) 746-3176.

Christine C. O'Day

Signature

Christine C. O'Day

(type or print name of person certifying)

application may be a reproduction of a properly executed, original notification. The original notice may either be sent to the Office of Enrollment and Discipline as notification to the Attorney's Roster of the change of address, or may be filed in one of the applications affected, provided that the notice includes an authorization for the public to inspect and copy the original notice in the event one of the applications containing a copy matures into a patent and the application containing the original paper is either pending or has become abandoned. Alternatively, the paper containing the original signature may be retained by applicant. See MPEP Section 502.02. The copies submitted in each affected application must identify where the original paper is located.

"Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4).

"See MPEP Section 711.03(c) for treatment of petitions to revive applications abandoned as a consequence of failure to timely receive an Office action addressed to the old correspondence address.

"The required notification of change of correspondence address need take no particular form. However, it should be provided in a manner calling attention to the fact that a change of address is being made. Thus, the mere inclusion, in a paper being filed for another purpose, of an address which is different from the previously provided correspondence address, without mention of the fact that an address change is being made would not ordinarily be recognized or deemed as instructions to change the correspondence address on the file record."

Please send all correspondence for this application as follows:

Peter F. Corless
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209

Please direct telephone calls to:

Peter F. Corless or Christine C. O'Day
Tel: (617) 439-4444
Fax: (617) 439-4170

Reg. No. 38,256

Tel. No. (617) 439-4444

Customer No. 21874

Christine C. O'Day
SIGNATURE OF PRACTITIONER

Christine C. O'Day
(type or print name of practitioner)

Edwards & Angell, LLP
P.O. Box 9169
P.O. Address

Boston, Massachusetts 02209

(Change of Attorney's Address in Application--page 2 of 2)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

21874 7590 02/06/2003

EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	15

DATE MAILED: 02/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev 07-01)

Office Action Summary	Application No.	Applicant(s)	
	09/700,094	MEESE ET AL.	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19-24 and 28-39* is/are pending in the application.

4a) Of the above claim(s) *11-14,21-24,31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1-10,15,16,18-20,28-30,32 and 34-39* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the invention of Group 1 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the European Patent Office did not find Unity of Invention to be lacking, and that examination of the subject matter of all of the inventions would not place an undue burden on the examiner. These arguments are not found persuasive because the USPTO is not beholden to any decisions made by a foreign patent office concerning unity of invention, nor is search burden a factor taken into consideration when a determination of Lack of Unity of Invention is made.

As stated in the Requirement for Election of Invention, the tolterodine skeleton, common to all of the claimed compounds, is a significant structural element shared by all of the alternatives. This structural element was known at the time the invention was made, and as such is not a special technical feature.

That the claimed compounds do not posses unity of invention for the reasons that when considered as a whole, there is no special technical feature common to all of the claimed compounds is further demonstrated hereinbelow:

The reference cited in the requirement for Election of Invention, mailed 7 September 2001, WO 94/11337 (Johansson et al), discloses at least two of the instantly claimed compounds.

Page 1 of the Johansson et al publication depicts a compound of formula I, wherein R^1 is methyl (2-methoxy), and on page 2, Johansson et al states that the -- CH_2OH group is preferably at the 5- position, corresponding to compounds of instant

claim 1 wherein R' is C_1-C_6 alkyl. Pages 12 and 13 disclose the 2-benzyloxy derivative, corresponding to compounds of instant claim 1 wherein R' is substituted or unsubstituted benzyl.

Compound (iv) in instant claim 15 was known at the time the invention was made, and is disclosed in Brynne et al, "Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity" J. Clin. Pharm. Ther. vol. 35(7), pages 287-295 (1997).

Figure 2 on page 291 of Brynne et al disclsoses a series of metabolites of tolterodine, one of which is "IIa," the 5-hydroxymethyl metabolite. The caption of figure 2 and the second full paragraph on page 291 state that all metabolites were also identified as glucuronides, which means the 5-hydroxymethyl glucuronide of tolterodine was identified by Brynne et al.

Applicant is reminded that the determination whether a group of Inventions is so linked as to form a single general inventive concept is be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.

The requirement for Election of Invention is hereby modified so as to include phenolic monoesters, benzylic monoesters, wherein R and R' are hydrogen, with the proviso that R and R' are not both hydrogen, and the "bis" dicarboxylic esters, such as the last 4 compounds specified in claim 4, and in claim 28, wherein R is hydrogen or alternative "b."

Claims 11-14,21-24,31 and 33 are withdrawn from consideration as being drawn to nonelected inventions.

The requirement is still deemed proper and is therefore **repeated** and **maintained**.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
Claim 4 recites the following four compounds:

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester, and

(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester

as the last four compounds in the claim.

There is insufficient antecedent basis for this limitation in claim 4, as claim 4 depends ultimately from claim 1, wherein an alkylcarbonyl-2-(3-dialkylamino)-1-phenylpropyl-1-(4-hydroxymethyl)phenyl ester group is not one of the possible identities for R'. Claim 4 is rejected under 35 U.S.C. 112, second paragraph.

Drawing

The Drawing is objected to for reasons given on the enclosed PTO-948 form.

Specification

The Specification is objected to for lack of a Brief Description of the Drawing.

Claim Objections/Allowable Subject Matter

Claims 1-10,15,16,18-20,28- 30,32 and 34-39 are objected to, as they contain nonelected subject matter, but would be allowable upon cancellation of nonelected subject matter.

Compounds of the elected invention are deemed allowable. The elected invention includes phenolic monoesters, benzylic monoesters, identical diesters, mixed diesters, "bis" dicarboxylic esters (last four compounds of instant claim 4 and compounds of formula VII' –claim 28-, wherein R is hydrogen or identity "b").

Claims directed to a pharmaceutical composition comprising compounds of the elected invention, method of antagonizing muscarinic receptors comprising contacting the receptor with a compound according to the elected invention, and a method of treating a disease in a mammal by antagonizing muscarinic receptors in the mammal comprising administering an amount of a composition according to the elected invention effective to diminish or eliminate symptoms of the disease will be allowed forthwith upon cancellation of nonelected subject matter.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (703) 305-2050. The examiner can normally be reached Monday-Friday from 7:00am to 3:30pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (703) 308-

4716. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

zt

Art Unit 1624

Notice of References Cited	Application/Control No. 09/700,094	Applicant(s)/Patent Under Reexamination MEESE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Brynne et al, "Pharmacokinetics and pharmacodynamics of tolterodine in man: a new drug for the treatment of urinary bladder overactivity" J. Clin. Pharm. Ther. vol. 35(7), pages 287-295 (1997).
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Form PTO 948 (Rev. 03/01) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 9/700,094

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

The drawing(s) filed (insert date) 1-2-01 are:

A. ☐ approved by the Draftsperson under 37 CFR 1.84 or 1.152

B. ☑ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be sumitted according to the instructions on the back of this notice.

1 DRAWINGS 37 CFR 1.84(a): Acceptable categories of drawings: Black ink Color

____ Color drawings are not acceptable until petition is granted. Fig(s) _____

____ Pencil and non black ink not permitted Fig(s) _____

2 PHOTOGRAPHS. 37 CFR 1.84(b)

____ 1 full-tone set is required. Fig(s) _____

____ Photographs may not be mounted 37 CFR 1.84(c)

____ Poor quality (half-tone) Fig(s) _____

3 TYPE OF PAPER. 37 CFR 1.84(e)

____ Paper not flexible, strong, white, and durable Fig(s) _____

____ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted Fig(s) _____

____ Mylar, velum paper is not acceptable (too thin). Fig(s) _____

4 SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes.

____ 21.0 cm by 29.7 cm (DIN size A4)

____ 21.6 cm by 27.9 cm (8 1/2 x 11 inches)

____ All drawing sheets not the same size. Sheet(s) _____

____ Drawings sheets not an acceptable size. Fig(s) _____

5. MARGINS. 37 CFR 1.84(g): Acceptable margins'

Top 2.5 cm Left 2.5cm Right 1.5 cm Bottom 1.0 cm SIZE: A4 Size

Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: 8 1/2 x 11

Margins not acceptable. Fig(s) _____

_____ Top (T) _____ Left (L)

_____ Right (R) _____ Bottom (B)

6 VIEWS. 37 CFR 1.84(h)

REMINDER: Specification may require revision to correspond to drawing changes.

Partial views. 37 CFR 1.84(h)(2)

____ Brackets needed to show figure as one entity. Fig(s) _____

____ Views not labeled separately or properly Fig(s) _____

____ Enlarged view not labeled separately or properly. Fig(s) _____

7. SECTIONAL VIEWS. 37 CFR 1.84 (h)(3)

____ Hatching not indicated for sectional portions of an object Fig(s) _____

____ Sectional designation should be noted with Arabic or Roman numbers. Fig(s) _____

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)

____ Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) _____

9. SCALE. 37 CFR 1.84(k)

____ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s) _____

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)

✓ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) 1

11 SHADING 37 CFR 1.84(m)

____ Solid black areas pale. Fig(s) _____

____ Solid black shading not permitted. Fig(s) _____

____ Shade lines, pale, rough and blurred. Fig(s) _____

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS 37 CFR 1.84(p)

✓ Numbers and reference characters not plain and legible. Fig(s) 1

____ Figure legends are poor. Fig(s) _____

____ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s) _____

____ English alphabet not used. 37 CFR 1.84(p)(2) Figs _____

____ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height 37 CFR 1.84(p)(3) Fig(s) _____

13. LEAD LINES. 37 CFR 1.84(q)

____ Lead lines cross each other. Fig(s) _____

____ Lead lines missing. Fig(s) _____

14 NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)

____ Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) _____

15. NUMBERING OF VIEWS. 37 CFR 1.84(u)

____ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) _____

16. CORRECTIONS. 37 CFR 1.84(w)

____ Corrections not made from prior PTO-948 dated _____

17. DESIGN DRAWINGS 37 CFR 1.152

____ Surface shading shown not appropriate. Fig(s) _____

____ Solid black shading not used for color contrast. Fig(s) _____

COMMENTS

REVIEWER J-CHASE DATE 9.4.01 TELEPHONE NO. 703305 8430

ATTACHMENT TO PAPER NO. _____

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

06/01/01

#16 E
PS

Docket No. 55647 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	C. Meese, et al.		
SERIAL NO.:	09/700,094	GROUP:	1624
FILED:	January 2, 2001	EXAMINER:	Z. Tucker
FOR:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

Sir:

AMENDMENT

Applicants are in receipt of the Office Action dated February 6, 2003. Kindly amend the above-identified application as follows.

IN THE SPECIFICATION

Kindly insert the following section header following the title on page 1:

B1 BACKGROUND OF THE INVENTION

Kindly insert the following section header on page 3, at line 16:

B2 SUMMARY OF THE INVENTION

Kindly insert the following section headers and text beginning at page 4, line 4:

BRIEF DESCRIPTION OF THE DRAWINGS

B3 FIG. 1 shows the formation of the active metabolite from different prodrugs by human liver S 9 (%) in 1 hour.

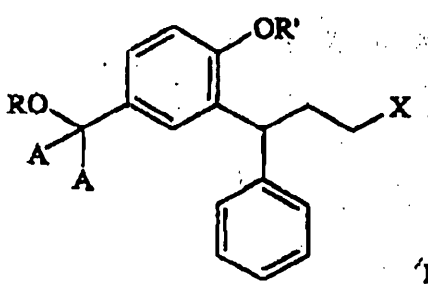
DETAILED DESCRIPTION OF THE INVENTION

IN THE CLAIMS

Please cancel non-elected claims 11-14, 21-24, 31 and 33, without prejudice or disclaimer.

Please amend claims 1, 4, 6, 15, 28, 34, 35 and 39 such that they read as follows:

1. A 3,3-Diphenylpropylamine of the general formula I:



Formula I

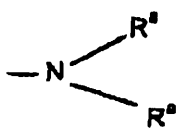
wherein R and R' are independently

a) hydrogen; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl;

with the proviso that R' is not hydrogen, methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent C_1-C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

B4

A represents hydrogen (^1H) or deuterium (^2H),

and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

4. The 3,3-Diphenylpropylamine as claimed in claim 2 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
B5 (±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and

(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester.

6. The 3,3-Diphenylpropylamine as claimed in claim 5 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,

(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,

(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

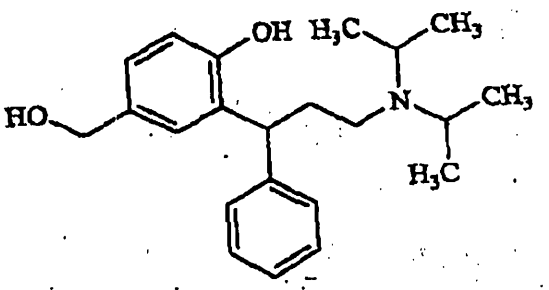
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,

cyclic oct-4-ene-1,8-dioate of Intermediate B,

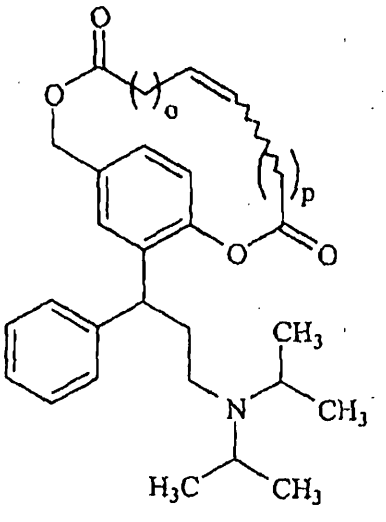
cyclic octane-1,8-dioate of Intermediate B, and

poly-co-DL-lactides of Intermediate B, said Intermediate B having the formula

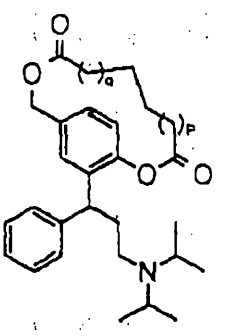


A 3,3-Diphenylpropylamine selected from

(i) compounds of the formulae IX and IX'



Formula IX



Formula IX'

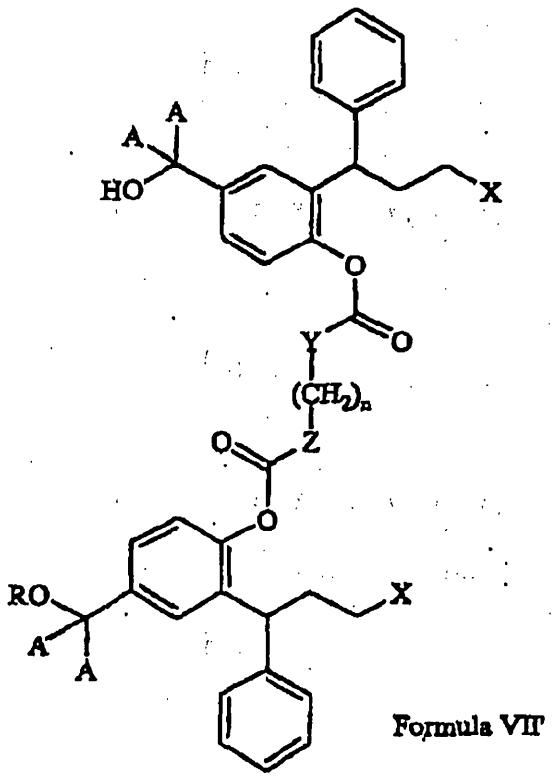
wherein o and p are the same or different and range from 0 to 6,

(ii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

16 A 3,3-Diphenylpropylamine of the general formula VII':



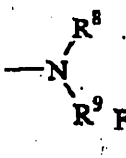
Formula VII'

wherein R is

a) hydrogen; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl;

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12, and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

20 ~~34~~. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1-10, ~~15~~ 11 and ~~28-30~~ 16-18 and a pharmaceutically acceptable carrier.

21 ~~35~~. A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims 1-10, ~~15~~ 11 and ~~28-30~~ 16-18.

39. A pharmaceutical composition of claim 34 wherein the composition is a patch formulation.

Kindly add the following new claims:

25, 40. (new) A 3,3-Diphenylpropylamine selected from:
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, and
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester.

26 41. (new) The 3,3-Diphenylpropylamine of claim 2, wherein the 3,3-Diphenylpropylamine is R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a pharmaceutically acceptable salt thereof.

REMARKS

Claims 11-14, 21-24, 31 and 33 have been cancelled without prejudice or disclaimer, as being drawn to a non-elected invention. Claims 1, 4, 6, 15, 28, 34, 35 and 39 have been amended, merely to cancel non-elected subject matter and to address minor informalities. Claims 40-41 have been added. The specification has been amended to provide several section headings as well as a "Brief Description of the Drawings" section.

No new matter has been added by virtue of these amendments. Support therefore can be found throughout the specification and in the original claims of the application. In particular, with respect to new claim 40, support can be found in original claim 4; support for new claim 41 also can be found in original claim 4 and at pages 11 and 62 of the specification.

Applicants appreciate the indication of allowable subject matter, i.e., that claims

1-10, 15, 16, 18-20, 28-30, 32 and 34-39 are merely objected to as containing non-elected subject matter, but would be allowable upon cancellation of that non-elected subject matter.

The Office Action further indicates that claims directed to a pharmaceutical composition comprising compounds of the elected invention, a method of antagonizing muscarinic receptors comprising contacting the receptor with a compound according to the elected invention, and a method of treating a disease in a mammal by antagonizing muscarinic receptors in the mammal comprising administering an amount of a composition according to the elected invention effective to diminish or eliminate symptoms of the disease also will be allowed upon cancellation of that non-elected subject matter.

Accordingly, Applicants submit the within amendment merely to cancel the non-elected subject matter from the claims and place those claims in condition for immediate allowance.

Additionally, claim 4 was rejected under 35 USC §112, second paragraph. As the rejection is understood, it is alleged that there is insufficient antecedent basis for the last four compounds in the claim. As grounds for the rejection, it is asserted that claim 1 (from which claim 4 depends) does not recite an alkylcarbonyl-2-(3-dialkylamino)-1-phenylpropyl-1-(4-hydroxymethyl)phenyl ester group as a possible R^1 identity.

Applicants submit that the within amendments obviate the §112, second paragraph, rejection. In particular, the last 4 compounds of claim 4 are presented as new independent claim 40. Thus, withdrawal of the rejection is requested.

The drawing was objected to for various informalities. Applicants will submit a replacement sheet for Figure 1 under separate cover, in order to correct those informalities.

The specification was objected to for lacking a section entitled "Brief Description of the Drawings". Applicants have amended the specification to add that section which includes a description of Figure 1 of the application. Additionally, the specification was further amended to recite other section headers, where appropriate, to conform to U.S. patent practice.

In view thereof, withdrawal of the objection to the specification is requested.

It is believed that the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,

Christine C. O'Day (Reg. 38,256)
John B. Alexander, Ph.D. (Reg. 48,399)
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P.O. Box 9169
Boston, MA 02209
(617) 439-4444

File History Content Report

The following content is missing from the original file history record obtained from the United States Patent and Trademark Office. No additional information is available.

Document Title: Amendment/Req. Reconsideration After Non-Final Rejection

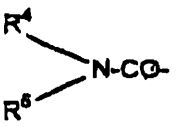
Document Date: 2003-04-14

Page(s): 11

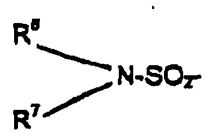
a) hydrogen[, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate]; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl;

[c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbouyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or



d) wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms or R^4 and R^5 form a ring together with the amine nitrogen; or



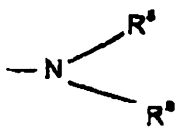
e) wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently C_1-C_4 alkyl or aryl,]

with the proviso that R' is not hydrogen, methyl or benzyl when R is hydrogen, and R is not ethyl when R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent C_1-C_6 alkyl groups, which may be the same or different and which together contain at least three carbon atoms, or R^8 and R^9 may form a ring together with the amine nitrogen,

A represents hydrogen (^1H) or deuterium (^2H),

and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

4. The 3,3-Diphenylpropylamine as claimed in claim 2 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
[(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,]

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, and

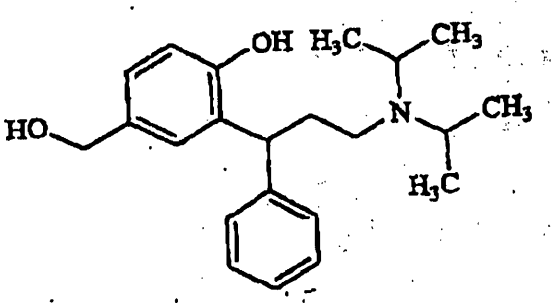
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester[,

(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester,

(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester].

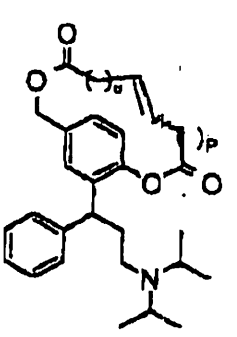
6. The 3,3-Diphenylpropylamine as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-one-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B, and
poly-co-DL-lactides of Intermediate B, said Intermediate B having the formula



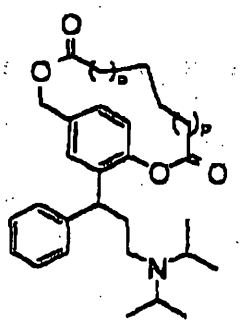
[wherein A is hydrogen (^1H) or deuterium (^2H)].

15. The 3,3-Diphenylpropylamine selected from:

(i) compounds of the formulae IX and IX'



Formula IX



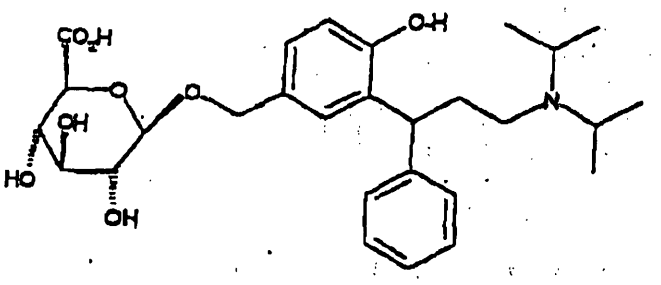
Formula IX'

wherein o and p are the same or different and range from 0 to 6,

(ii) [(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii)] Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

[(iv) (±) -2- (3-Diisopropylamino-1-phenylpropyl) -4- (1β-D-glucuronosyloxymethyl)-phenol having the formula

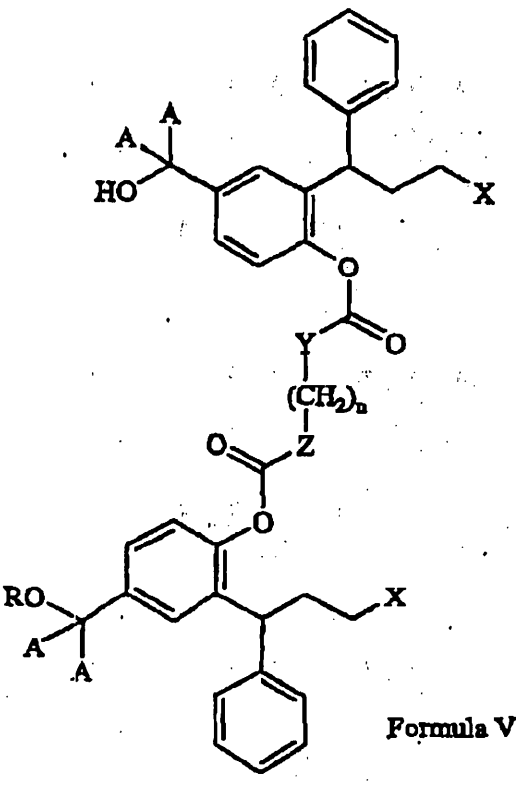


]

and

their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

28. A 3,3-Diphenylpropylamine of the general formula VII':



Formula VII'

wherein R is

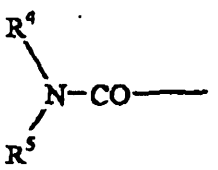
a) hydrogen[, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate]; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl; [or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

[redacted]

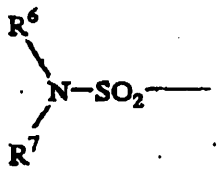
d)



wherein R^4 and R^5 independently

represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

e)



wherein R^6 and R^7 independently

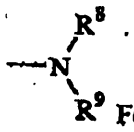
represent C_1-C_6 alkyl, substituted or unsubstituted aryl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c, are independently selected from C_1-C_4 alkyl or aryl,

with the proviso that R′ is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R′ is hydrogen,]

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,
A represents hydrogen (^1H) or deuterium (^2H),
n is 0 to 12, and
their salts with physiologically acceptable acids, their free bases and, when the compounds are in the form of optical isomers, the racemic mixture and the individual enantiomers.

34. A pharmaceutical composition comprising a 3,3-diphenylpropylamine according to any one of claims 1-10, 15 and 28-30 [31] and a pharmaceutically acceptable carrier.

35. A method of antagonizing a muscarinic receptor, the method comprising contacting the receptor with a compound according to any one of claims 1-10, 15 and 28-30 [31].

39. A pharmaceutical composition of claim [26] 34 wherein the composition is a patch formulation.

The following new claims were added:

40. (new) A 3,3-Diphenylpropylamine selected from:
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl] ester, and
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl] ester.

41. (new) The 3,3-Diphenylpropylamine of claim 2, wherein the 3,3-Diphenylpropylamine is R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester or a pharmaceutically acceptable salt thereof.

#170

Docket No. 5564

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	C. Meese, et al.		
SERIAL NO.:	09/700,094	GROUP:	1624
FILED:	January 2, 2001	EXAMINER:	Z. Tucker
FOR:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

Sir:

SUPPLEMENTAL AMENDMENT

Applicants are in receipt of the Office Action dated February 6, 2003. Kindly amend the above-identified application as follows.

IN THE DRAWINGS:

Kindly enter the enclosed replacement drawing sheet for Figure 1 (sheet 1/1).

Ok to enter MM

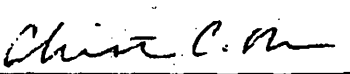
REMARKS

The within Supplemental Amendment is submitted merely to provide a suitable formal drawing for the application. No new matter is presented by virtue of the within amendment.

By way of history, the Office Action mailed on February 6, 2003, indicated that the drawing (Figure 1) was objected to with reference to the PTO-948 form. Applicants filed a timely response to that Office Action on April 14, 2003, and addressed each of the rejections and objections of record. In Applicants' response, it was indicated that a suitable formal drawing would be provided under separate cover. Accordingly, Applicants herewith provide such drawing, thus obviating the objection.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



Christine C. O'Day (Reg. 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. (617) 439-4444

VERSION WITH MARKINGS TO SHOW CHANGES

IN THE DRAWINGS:

A replacement drawing sheet for Figure 1 (sheet 1/1) was submitted to replace the earlier filed drawing.

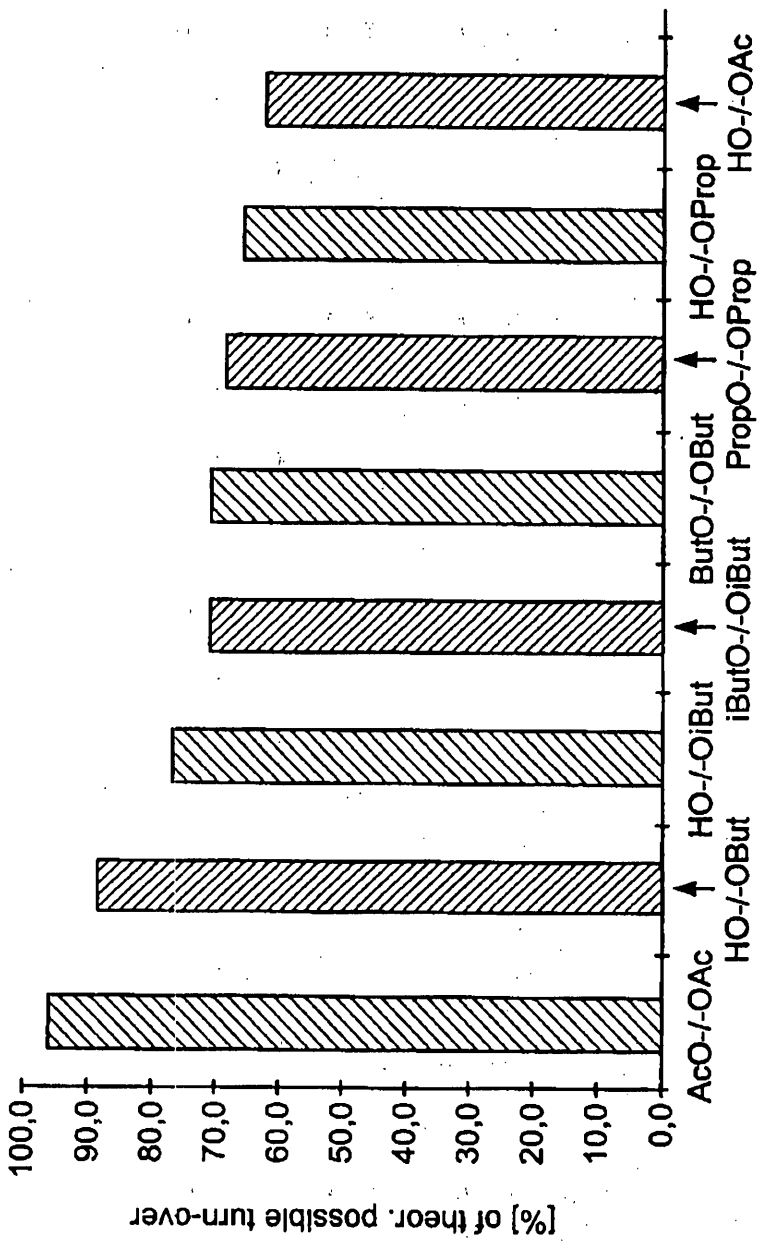


FIG.1

Notice of Allowability	Application No. 09/700,094	Applicant(s) MEESE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address*--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *14 April 2003*.
2. ☒ The allowed claim(s) is/are *1-10,15,16,18-20,28-30,32,34-38,40 and 41*.
3. ☒ The drawings filed on *28 April 2003* are accepted by the Examiner.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

8. ☐ CORRECTED DRAWINGS must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet.

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☒ Notice of References Cited (PTO-892)
2☐ Notice of Informal Patent Application (PTO-152)
3☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
4☐ Interview Summary (PTO-413), Paper No.____ .
5☐ Information Disclosure Statements (PTO-1449), Paper No. ____.
6☒ Examiner's Amendment/Comment
7☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
8☒ Examiner's Statement of Reasons for Allowance
9☐ Other .

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Christine C. O'Day on 28 April 2003.

IN THE CLAIMS –

Claim 39 has been cancelled.

Response to Amendment

The amendments to the specification have been entered. The amendments to claims 1,4, 6, 15, 28, 34 and 35 have been entered. Claims 40 and 41 have been added. Claims 11-14, 21-24, 31 and 33, directed to non-elected subject matter, have been cancelled. Claim 39 has been cancelled by Examiner's Amendment, authorized by applicant.

Allowable Subject Matter

Claims 1-10,15,16,18-20,28-30, 32, 34-38, 40 and 41 are allowed.

The following is an examiner's statement of reasons for allowance:

Applicant has cancelled all non-elected subject matter.

The compounds of claims 1-10, 15, 28-30, 40 and 41 are not disclosed in the prior art, nor is there any express suggestion in the prior art that would render said compounds obvious to make. Therefore, a process for preparing compounds of the invention, compositions comprising said compounds, a method of antagonizing a muscarinic receptor with, and a method of treating a muscarinic receptor mediated condition with these compounds are novel and unobvious.

The compounds of the invention are novel derivatives of tolterodine, a known compound. The state of the art as it pertains to tolterodine derivatives is exemplified by the following four references:

Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology, vol. 81, pages 169-172 (1997).

Nilvebrant et al, "Tolterodine - A New Bladder Selective Muscarinic Receptor Antagonist: Preclinical Pharmacological and Clinical Data" Life Sciences, vol. 60(13/14), pages 1129-1136 (1997).

Postlind et al, "Tolterodine, A New Muscarinic Receptor Antagonist, is Metabolized by Cytochromes P450 and 3A in Human Liver Microsomes" Drug Metabolism and Disposition, vol. 26(4), pages 289-293 (1998).

Andersson et al, "Biotransformation of Tolterodine, A New Muscarinic Receptor Antagonist, in Mice, Rats, and Dogs" Drug Metabolism and Disposition, vol. 26(6), pages 528-535 (1998).

The two Nilvebrant et al references disclose that the 5-hydroxymethyl metabolite of tolterodine contributes significantly to the therapeutic efficacy of tolterodine.

The Postlind et al reference explores the effects of concomitantly administered drugs on the metabolism of tolterodine in human liver microsomes.

The Andersson et al reference describes several distinct tolterodine derivatives formed in the metabolism of that compound by mice, rats and dogs.

None of the aforementioned references disclose an ester derivative of tolterodine, or that an ester derivative of tolterodine would be an effective therapeutic agent.

With regard to the method of claim 36, the instant specification, on page 36, states that diseases amenable to treatment by antagonizing muscarinic receptors in a mammal refers to spasmogenic conditions that are caused by muscarinic mechanisms.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

All Post-Allowance Correspondence concerning this application must be mailed to:

BOX ISSUE FEE
COMMISSIONER FOR PATENTS
WASHINGTON, DC 20231

Or you can fax them to the Office of Patent Publications at 703-308-5083, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027. The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.
:t

Mukund J. Shah

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

Notice of References Cited	Application/Control No. 09/700,094	Applicant(s)/Patent Under Reexamination MEESE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	I	US-			
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	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology, vol. 81, pages 169-172 (1997).
	V	Nilvebrant et al, "Tolterodine - A New Bladder Selective Muscarinic Receptor Antagonist: Preclinical Pharmacological and Clinical Data" Life Sciences, vol. 60(13/14), pages 1129-1136 (1997).
	W	Postlind et al, "Tolterodine, A New Muscarinic Receptor Antagonist, is Metabolized by Cytochromes P450 and 3A in Human Liver Microsomes" Drug Metabolism and Disposition, vol. 26(4), pages 289-293 (1998).
	X	Andersson et al, "Biotransformation of Tolterodine, A New Muscarinic Receptor Antagonist, in Mice, Rats, and Dogs" Drug Metabolism and Disposition, vol. 26(6), pages 528-535 (1998).

*A copy of this reference is not being furnished with this Office action (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign

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NOTICE OF ALLOWANCE AND FEE(S) DUE

21874 7590 05/16/2003

EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**CLASS-SUBCLASS**
1624	514-175000

DATE MAILED: 05/16/2003

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$0	$1300	08/18/2003

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
Alexandria, Virginia 22313-1450
Fax (703)746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

21874 7590 05/16/2003

EDWARDS & ANGELL, LLP
P O. BOX 9169
BOSTON, MA 02209

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1300	$0	$1300	08/18/2003

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-175000

1 Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE. Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) ☐ individual ☐ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed.

☐ Issue Fee

☐ Publication Fee

☐ Advance Order - # of Copies _____

4b Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Commissioner is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____(enclose an extra copy of this form).

Commissioner for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
PO Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

21874 7590 05/16/2003

EDWARDS & ANGELL, LLP
P O. BOX 9169
BOSTON, MA 02209
UNITED STATES

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/16/2003

Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The patent term extension is 0 days. Any patent to issue from the above identified application will include an indication of the 0 day extension on the front page.

If a continued prosecution application (CPA) was filed in the above-identified application, the filing date that determines patent term extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system. (http://pair.uspto.gov)

Any questions regarding the patent term extension or adjustment determination should be directed to the Office of Patent Legal Administration at (703)305-1383.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

21874 7590 05/16/2003

EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209
UNITED STATES

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 05/16/2003

Notice of Fee Increase on January 1, 2003

If a reply to a "Notice of Allowance and Fee(s) Due" is filed in the Office on or after January 1, 2003, then the amount due will be higher than that set forth in the "Notice of Allowance and Fee(s) Due" since there will be an increase in fees effective on January 1, 2003. See Revision of Patent and Trademark Fees for Fiscal Year 2003: Final Rule, 67 Fed. Reg. 70847, 70849 (November 27, 2002).

The current fee schedule is accessible from: http://www.uspto.gov/main/howtofees.htm.

If the issue fee paid is the amount shown on the "Notice of Allowance and Fee(s) Due," but not the correct amount in view of the fee increase, a "Notice to Pay Balance of Issue Fee" will be mailed to applicant. In order to avoid processing delays associated with mailing of a "Notice to Pay Balance of Issue Fee," if the response to the Notice of Allowance and Fee(s) due form is to be filed on or after January 1, 2003 (or mailed with a certificate of mailing on or after January 1, 2003), the issue fee paid should be the fee that is required at the time the fee is paid. If the issue fee was previously paid, and the response to the "Notice of Allowance and Fee(s) Due" includes a request to apply a previously paid issue fee to the issue fee now due, then the difference between the issue fee amount at the time the response is filed and the previously paid issue fee should be paid. See Manual of Patent Examining Procedure, Section 1308.01 (Eighth Edition, August 2001).

Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (REV. 05-03) Approved for use through 04/30/2004.

OIPE
AUG 1 8 2003
PATENT & TRADEMARK OFFICE

3

2CE/16 #20 05/29/03

Practitioner's Docket No. 55647 (45107)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese, et al.

SERIAL NO.: 09/700,094 GROUP: 1624

FILED: January 2, 2001 EXAMINER: Z. Tucker

FOR: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

RECEIVED
AUG 20 2003
TECH CENTER 1600/2900

Mail Stop: RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Match and Return

REQUEST FOR CONTINUED EXAMINATION (RCE)
(37 C.F.R. 1.114)

1. Applicant hereby requests continued examination, in accordance with 37 C.F.R. Section 1.114, for the above identified application.

CERTIFICATION UNDER 37 C.F.R. SECTIONS 1.8(a) AND 1.10
(When using Express Mail, the Express Mail label number is mandatory; Express Mail certification is optional.)

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

[X] deposited with the United States Postal Service in an envelope addressed to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

37 C.F.R. Section 1.8(a)		37 C.F.R. Section 1.10
[X]	with sufficient postage as first class mail.	[ ] as "Express Mail Post Office to Addressee" Mailing Label No. (mandatory)

TRANSMISSION

[ ] facsimile transmitted to the Patent and Trademark Office (703) ___-_____

Date: 8/14/03

Susan M Dillon
Signature

Susan M. Dillon
(type or print name of person certifying)

08/19/2003 MBIZUNES 00000048 09700094
01 FC:1801 750.00 OP

WARNING: *35 U.S.C. 132(b) and Section 1.114 provide for the continued examination of an application and not examination of a continuing application). Accordingly, the Office will not permit an applicant to obtain continued examination on the basis of claims that are independent and distinct from the claims previously claimed and examined. Notice of March 10, 2000, 65 Fed Reg 14865, at 14868.*

WARNING: *A continued examination request cannot be made if at least one office action under 35 U.S.C. 132 or a notice of allowance under 35 U.S.C. 161 has not been mailed. The provisions of 37 C.F.R. 1.114 also do not apply (1) to a provisional application, an application for a utility or plant patent filed under 35 U.S.C. 111(a); (2) an international application filed under 35 U.S.C. 363 before June 8, 1995; (3) a patent under reexamination; or (4) an application for a design patent. 37 C.F.R. Section 1.114(d).*

NOTE: *There is no limit to the number of times the fee for continued examination may be submitted. Notice of March 10, 2000, 65 Fed Reg 14865, at 14868.*

NOTE: *Unlike a continuation application, a continued examination request can utilize the mailing procedure of 37 C.F.R. 1.8. See 37 C.F.R. Section 1.8(a)(2)(i)(A).*

TIME REQUEST IS BEING MADE

2. This request is being submitted *(check appropriate item(s) below)*:

i. [X] Prior to abandonment of the application

ii. [X] In lieu of payment of the issue fee
- [X] Prior to payment of issue fee
- [ ] Issue fee has been paid but a petition under Section 1.313 has been filed herewith

iii. [ ] Prior to a decision on appeal to the Board of Patent Appeals & Interferences
- [ ] A notice is being separately sent to the Board of Patent Appeals & Interferences that this Request for Continued Examination is being filed.

NOTE: *If such a notice is not sent to the Board, they may refuse to vacate a decision rendered after the filing of the RCE but before recognition by the Office of the RCE request under Section 1.114.*

iv. [ ] Appeal to the U.S. Court of Appeals of the Federal Circuit under 35 U.S.C. 145 or [ ]Commencement of a civil action under 35 U.S.C. 146
- [ ] Prior to the filing of such appeal or commencement of civil action
- [ ] Such appeal or commencement of civil action has been terminated

ENCLOSURES

3. Enclosed herewith is/are:

WARNING: *If reply to a final or non-final Office action under 35 U.S.C. 132 is outstanding, the submission must meet the reply requirements of Section 1.111. 37 C.F.R. Section 1.114(b).*

[X] An information disclosure (37 C.F.R. Section 1.98)
- [X] Form PTO-1449 (PTO/SB/08A and 08B)

[ ] A Response
[ ] New arguments

[ ] New evidence in support of patentability

[ ] Other:

FEE FOR REQUEST (37 C.F.R. Section 1.17(e)).

4. This application is on behalf of:

[ ]	Small entity (and status is still as small entity)	$ 375.00
[X]	Other than a small entity	$750.00

Continued Prosecution Request Fee $ 750.00

FEE FOR CLAIMS

NOTE: *"The fee for continued examination under Section 1.114 (Section 1.17(e)) does not include additional claims fee (cf. 1.53 (d)(3)(ii))." See Notice of March 10, 2000, 65 Fed Reg 14865, at 14868.*

37 C.F.R. 1.53(d)(3) : "The filing fee for a continued prosecution application filed under this paragraph is:

(i) The basic filing fee as set forth in Section 1.16; and

(ii) Any additional Section 1.16 fee due based on the number of claims remaining in the application after entry of any amendment accompanying the request for an application under this paragraph and entry of any amendments under Section 1.116 unentered in the prior application which applicant has requested to be entered in the continued prosecution application."

5. The fee for claims (37 C.F.R. Section 1.16(b)-(d)) has been calculated as shown below:

(Col.1)		(Col. 2)	(Col. 3)	SMALL ENTITY			OTHER THAN A SMALL ENTITY		
Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra		Rate	Addit. Fee	*OR*	Rate	Addit. Fee
Total	*	Minus	**	=	x $9 =	$		x $18 =	$
Indep.	*	Minus	***	= 0	x $39 =	$		x $84 =	$ 0
[ ] First Presentation of Multiple Dependent Claim					+ $130 =	$		+ $280 =	$ 0
					Total Addit. Fee	$	*OR*	Total Addit. Fee	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3,

** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest No. Previously Paid For" (Total or Indep.) is the highest number found in the appropriate box in Col. 1 of a prior amendment or the number of claims originally filed.

WARNING: *See 37 C.F.R. Section 1.116.*

(complete (c) or (d), as applicable)

(c) [X] No additional fee is required.

OR

(d) [ ] Total additional fee required is $ _____.

EXTENSION OF TIME

(If an extension of time is appropriate complete (a) or (b), as applicable)

6. The proceedings herein are for a patent application, and the provisions of 37 C.F.R. Section 1.136(a) apply.

(a) [ ] Applicant petitions for an extension of time, the fees for which are set out in 37 C.F.R. Section 1.17(a)(1)-(4), for the total number of months checked below:

Extension for (months)	Fee for other than small entity	Fee for small entity
[ ] one month	$110.00	$ 55.00
[ ] two months	$410.00	$205.00
[ ] three months	$930.00	$465.00
[ ] four months	$1,450.00	$725.00
[ ] five months	$1,970.00	$985.00

Fee $____

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured, and the fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $____

OR

(b) [X] Applicant believes that no extension of time is required. However, this is a conditional petition and authorization to pay the necessary fees to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

TOTAL FEE(S) DUE

WARNING: *The fee for continued examination under Section 1.114 may not be deferred. 37 C.F.R. Section 1.53(f).*

7. The total fee(s) due is/are:

Continued Prosecution Fee (Section 1.17(e)) $ 750.00

Fee(s) for additional claims (if any) (Section 1.16(b)-(d)) $ _____
Extension of time fee (if any) (Section 1.17(a)(1)-(4)) $ _____

Total Fee(s) Due: $ 750.00

PAYMENT OF FEE(S) DUE

8. Please pay the fee(s) for this continued examination application as follows:

[X] Check are attached for the sum of $ 750.00

[ ] Charge Account _____ the sum of $ _____

[ ] Charge Credit Card the sum of $ _____
(Credit Card Payment Form (PTO-2038) attached.)

Please charge any required additional fee(s) for Section 1.17(e), Section 1.16(b)-(d) and/or Section 1.17(a)(1)-(4) to

[X] Account 04-1105

[ ] Credit Card (Credit Card Payment Form (PTO-2038) attached.)

INVENTORSHIP

NOTE: *Any change of inventors must be via the procedure set forth in 37 C.F.R. Section 1.48. See Notice of March 10, 2000, 65 Fed Reg 14865, at 14868.*

9. This application as amended names as inventors:

[ ] the same inventors as previously designated for the claims.

[ ] fewer than the inventors previously designated and a statement accompanies this request for the deletion of the name or names of the person or persons who are not inventors of the invention now being claimed.

[ ] a person not named previously as an inventor and a petition under 37 C.F.R. Section 1.48 is/has separately:
[ ] being filed
[ ] been filed

Christine C. O'Day
SIGNATURE OF PRACTITIONER

Reg. No.: 38,256

Christine C. O'Day
(type or print name of practitioner)

Tel. No.: (617) 439-4444

Edwards & Angell, LLP
P.O. Box 9169, Boston, MA 02209
P.O. Address

Customer No.: 21874

#21
10/29/03
C. Stiefel

Docket No. 55647 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: C. Meese et al.

Serial No.: 09/700,094 GROUP: 1624

Filed: January 2, 2001 EXAMINER: Z. Tucker

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Mail Stop: RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

****

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date 8/14/03 By: Susan M Dillon
Susan M. Dillon

****

Sir:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the provisions of 37 C.F.R. §§1.56 and 1.97, Applicants herewith submit the publications and/or patents shown on the attached form PTO-1449, for consideration by the Examiner in connection with the examination of the above-identified patent application.

REMARKS

In accordance with the provisions of 37 C.F.R. §1.97, this statement is being filed:

_X_ (1) within three (3) months of the Filing Date or **before the mailing date of the First Office Action** on the merits; or

____ (2) within three months of the mailing date of the Written Opposition issued by the: _____Patent Office (dated _____); or

[redacted]

___ (3) after the period defined in (1) but before the mailing date of a Final Rejection or Notice of Allowance, and the requisite Certification or fee under Rule 1.17(p), namely $180.00, is included herein; or

___ (4) after the mailing date of a Final Rejection or Notice of Allowance but before the payment of the Issue Fee, and the requisite Certification, petition, and petition fee are included herein.

It is respectfully requested that each of the documents shown on the attached form(s) PTO-1449 be made of record in this application. Copies of these documents (CHECK ONE):

_X_ are enclosed herewith; or

___ have been cited in the parent application, and are thus not being resubmitted herein.

Early examination and allowance of the present application are respectfully solicited.

FEE AUTHORIZATION

Should any fees associated with the submission be required, the Commissioner is authorized to charge the missing fee to our Deposit Account, No. 04-1105. Any overpayments should be credited to said Deposit Account.

Respectfully submitted,

Christine C. O'Day (Reg. 38,256)
Edwards & Angell, LLP
PO Box 9169
Boston, MA 02209
(617) 439-4444

Date: August 14, 2003

FORM PTO-1449	DOCKET NO.: 55647	SERIAL NO.: 09/700,094
INFORMATION DISCLOSURE STATEMENT	APPLICANT(S): C. Mees . et al.	
	FILING DATE: January 2, 2001	GROUP NO.: 1624

UNITED STATES PATENT DOCUMENTS

EXAM. INITIALS		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
ZT	AA	6,313,132 B1	11/6/01	R. Johansson, et al.	514	277	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES/NO

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

Examiner: Zachary	Date: 29 OCTOBER 2003

Notice of Allowability	Application No. 09/700,094	Applicant(s) MEESE ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- ***The MAILING DATE of this communication appears on the cover sheet with the correspondence address***--
claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

☒ This communication is responsive to *18 August 2003*.
☒ The allowed claim(s) is/are *1-10,15,16,18-20,28-30,32,34-38,40 and 41*.
☒ The drawings filed on *28 April 2003* are accepted by the Examiner.
☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: _____.
☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
(a) ☐ The translation of the foreign language provisional application has been received.
☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**

☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF FORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

☐ CORRECTED DRAWINGS must be submitted.
(a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
1) ☐ hereto or 2) ☐ to Paper No. ____.
(b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
(c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet.

☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. Notice of References Cited (PTO-892)
2. ☐ Notice of Informal Patent Application (PTO-152)
3. Notice of Draftperson's Patent Drawing Review (PTO-948)
4. ☐ Interview Summary (PTO-413), Paper No.____ .
5. Information Disclosure Statements (PTO-1449), Paper No. *21*.
6. ☐ Examiner's Amendment/Comment
7. Examiner's Comment Regarding Requirement for Deposit of Biological Material
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other

Page 1 of 2

Response to Request for Continued Examination

The claims have not been amended. A supplemental Information Disclosure Statement has been submitted, citing one reference, US 6,313,132 B1 (Johannson et al).

This reference does not anticipate nor render obvious any of the instantly claimed compounds, compositions, or method. Compounds of instant claim 1 cannot be constructed from the genus in the section headed "Summary of the Invention" in Johannson et al. The cyclic diesters of the instant application and the dimeric compounds claimed herein are not touched upon by Johansson et al either.

Claims 1-10,15,16,18-20,28-30,32,34-38,40 and 41 are allowed.

Conclusion

All Post-Allowance Correspondence concerning this application must be mailed to:

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-308-5083, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027. The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.

zt

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

JOHN M. FORD
PRIMARY EXAMINER
GROUP - ART UNIT 1624

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P O Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21874 7590 11/04/2003

EDWARDS & ANGELL, LLP
P O. BOX 9169
BOSTON, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/04/2003

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	02/04/2004

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 10/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

2174 7590 11/04/2003

EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209

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Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	02/04/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-175000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☐ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☐ Issue Fee
☐ Publication Fee
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached
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Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

21874 7590 11/04/2003

EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 11/04/2003

Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 10/03) Approved for use through 04/30/2004.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

21814 7590 11/04/2003

EDWARDS & ANGELL, LLP
P.O. BOX 9169
BOSTON, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/04/2003

Notice of Fee Increase on October 1, 2003

a reply to a "Notice of Allowance and Fee(s) Due" is filed in the Office on or after October 1, 2003, then the ount due will be higher than that set forth in the "Notice of Allowance and Fee(s) Due" since there will be an rease in fees effective on October 1, 2003. See Revision of Patent Fees for Fiscal Year 2004; Final Rule, 68 Fed. g. 41532, 41533, 41534 (July 14, 2003).

e current fee schedule is accessible from (http://www.uspto.gov/main/howtofees.htm).

the fee paid is the amount shown on the "Notice of Allowance and Fee(s) Due" but not the correct amount in view the fee increase, a "Notice of Pay Balance of Issue Fee" will be mailed to applicant. In order to avoid processing lays associated with mailing of a "Notice of Pay Balance of Issue Fee," if the response to the Notice of Allowance to be filed on or after October 1, 2003 (or mailed with a certificate of mailing on or after October 1, 2003), the ue fee paid should be the fee that is required at the time the fee is paid. If the issue fee was previously paid, and the sponse to the "Notice of Allowance and Fee(s) Due" includes a request to apply a previously-paid issue fee to the ue fee now due, then the difference between the issue fee amount at the time the response is filed and the eviously-paid issue fee should be paid. See Manual of Patent Examining Procedure, Section 1308.01 (Eighth ition, August 2001).

fective October 1, 2003, 37 CFR 1.18 is amended by revising paragraphs (a) through (c) to read as set forth below.

ction 1.18 Patent post allowance (including issue) fees.

Issue fee for issuing each original or reissue patent, ept a design or plant patent:
By a small entity (Sec. 1.27(a)) $665.00
By other than a small entity $1,330.00

Issue fee for issuing a design patent:
By a small entity (Sec. 1.27(a)) $240.00
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ssue fee for issuing a plant patent:
ly a small entity (Sec. 1.27(a)) $320.00
y other than a small entity $640.00

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(Rev. 10/03) Approved for use through 04/30/2004.

6/14

Attorney's Docket No. 55647 (45107) *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Claus Meese
Application No.: 09/700,094 Group No.: 1624
Filed: July 2, 2001 Examiner: Tucker, Zachary C.

For: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
MAIL STOP ISSUE FEE

TRANSMITTAL OF PAYMENT OF ISSUE FEE (37 C.F.R. SECTION 1.311)

1. Applicant hereby pays the issue fee for the attached Issue Fee Transmittal PTOL-85.

2. Fee (37 C.F.R. section 1.18(a) and (b)):

Application status is:	Regular	Design
[ ] small business entity fee	[ ] $ 665.00	[ ] $240.00
[X] other than a small entity fee	[X]$1,330.00	[ ] $480.00
3. Publication fee	[ ] $ 300.00	
4. Advanced order of soft copies of patent fee	[X] $ 30.00	
	Total Fee Enclosed:	$ 1,360.00

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Date: January 26, 2004

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☐ transmitted by facsimile to the Patent and Trademark Office.

Elena Misiaszek
Signature

Elena Misiaszek
(type or print name of person certifying)

5. Payment of fee:

[X] Enclosed please find a check in the amount of $ 1,360.00

[X] Charge Account 04-1105 for any fee deficiency.

[ ] Charge Account _____ the sum of $ _____.

A duplicate of this request is attached.

Christine C. O'Day
SIGNATURE OF PRACTITIONER

Reg. No. 38,256

Christine C. O'Day
(type or print name of practitioner)

Tel. No. (617) 439-4444

EDWARDS & ANGELL, LLP
P.O. Box 55874
P.O. Address

Customer No. 21874

Boston, Massachusetts 02205

431288

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

21874 7590 11/04/2003

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P.O. BOX 9169
BOSTON, MA 02209

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Certificate of Mailing or Transmission
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Elena Misiaszek	(Depositor's name)
Elena Misiaszek	(Signature)
1/26/04	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,094	01/02/2001	Claus Meese	MBHB00-1121	1408

TITLE OF INVENTION: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	02/04/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-175000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47, Rev 03-02 or more recent) attached. Use of a Customer Number is required.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Edwards & Angell, LLP
2 Peter F. Corless
3 Christine C. O'Day

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Schwarz Pharma AG

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Monheim, FederRepGermany

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ individual ☒ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:
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(Authorized Signature)	(Date)
Christine C. O'Day	1-26-04

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02/02/2004 HBENE1 00000032 09700094
01 FC:1501 1330.00 OP
02 FC:1801 30.00 OP

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#24
CA
2-18-04

Docket No. 55647 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: C. Meese et al.

SERIAL NO.: 09/700,094 GROUP: 1624

FILED: January 2, 2001 EXAMINER: Z. Tucker

FOR: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Commissioner for Patents and Trademarks
Washington, D.C. 20231

SIR:

CHANGE OF ATTORNEY'S ADDRESS IN APPLICATION

NOTE: Section 601.03 (Change of Correspondence Address), M.P.E.P., 7th Edition states:

"Where an attorney or agent of record (or applicant, if he or she is prosecuting the application pro se) changes his or her correspondence address, he or she is responsible for promptly notifying the Patent and Trademark Office of the new correspondence address (including ZIP code number). The notification should also include his or her telephone number. A change of correspondence address may not be signed by an attorney or agent not of record (see MPEP Section 405).

"Unless the correspondence address is designated as the address associated with a Customer Number, a separate notification must be filed in each application for which a person is intended to receive communications from the Office. See MPEP Section 403 for Customer Number Practice. In those instances where a change in the correspondence address of a registered attorney or agent is necessary in a plurality of applications, the notification filed in each

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CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. Section 1.8(a))

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[ ] transmitted by facsimile to the Patent and Trademark Office (703) 746.3176.

Elena Miaszek
Signature

Date: 1/26/04

Elena Miaszek
(type or print name of person certifying)

application may be a reproduction of a properly executed, original notification. The original notice may either be sent to the Office of Enrollment and Discipline as notification to the Attorney's Roster of the change of address, or may be filed in one of the applications affected, provided that the notice includes an authorization for the public to inspect and copy the original notice in the event one of the applications containing a copy matures into a patent and the application containing the original paper is either pending or has become abandoned. Alternatively, the paper containing the original signature may be retained by applicant. See MPEP Section 502.02. The copies submitted in each affected application must identify where the original paper is located.

"Special care should be taken in continuation or divisional applications to ensure that any change of correspondence address in a prior application is reflected in the continuation or divisional application. For example, where a copy of the oath or declaration from the prior application is submitted for a continuation or divisional application filed under 37 CFR 1.53(b) and the copy of the oath or declaration from the prior application designates an old correspondence address, the Office may not recognize, in the continuation or divisional application, the change of correspondence address made during the prosecution of the prior application. Applicant is required to identify the change of correspondence address in the continuation or divisional application to ensure that communications from the Office are mailed to the current correspondence address. 37 CFR 1.63(d)(4).

"See MPEP Section 711.03(c) for treatment of petitions to revive applications abandoned as a consequence of failure to timely receive an Office action addressed to the old correspondence address.

"The required notification of change of correspondence address need take no particular form. However, it should be provided in a manner calling attention to the fact that a change of address is being made. Thus, the mere inclusion, in a paper being filed for another purpose, of an address which is different from the previously provided correspondence address, without mention of the fact that an address change is being made would not ordinarily be recognized or deemed as instructions to change the correspondence address on the file record."

Please send all correspondence for this application as follows:

Peter F. Corless
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205

Please direct telephone calls to:

Peter F. Corless or Christine C. O'Day
Tel: (617) 439-4444
Fax: (617) 439-4170

Reg. No. 38,256

Tel. No. (617) 439-4444

Customer No. 21874

Chris C.O.

SIGNATURE OF PRACTITIONER

Christine C. O'Day
(type or print name of practitioner)

Edwards & Angell, LLP
P.O. Box 55874
P.O. Address

Boston, Massachusetts 02205

6713.64

COMPLETED

1624
OCS

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER		Docket Number: MBHB00-1121 (New Atty. Docket No.: 12961/46101)	
Application Number: 09/700,094	Filing Date: January 02, 2001	Examiner: Zachary C. TUCKER	Art Unit: 1624
Patent Number: 6,713,464	Issue Date: March 30, 2004		
Invention Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		Inventor(s): Claus MEESE et al.	

Address to:
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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Date: AUGUST 29, 2005

Signature: Joseph A Coppola

Joseph A. Coppola (Reg. No. 38,413)

Sir:

Transmitted herewith for filing in the above-identified patent application is a Power of Attorney by Assignee of Entire Interest (Revocation of Prior Powers and Appointment of New Power) and 3.73(b) statement. Please note that two (2) copies are being submitted, each signed by separate authorized representatives of the assignee.

Please record the Power and change of address in the above application.

In addition, please change the Attorney Docket Number for the above-identified patent application from "MBHB00-1121" to -- **12961/46101** --.

Dated: AUGUST 29, 2005

By: Joseph A Coppola
Joseph A. Coppola (Reg. No. 38,413)

KENYON & KENYON
One Broadway
New York, N.Y. 10004
(212) 425-7200 (telephone)
(212) 425-5288 (facsimile)
Customer No. 26646

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		
REVOCATION OF PRIOR POWER OF ATTORNEY and APPOINTMENT OF NEW POWER OF ATTORNEY BY ASSIGNEE and 3.73(b) STATEMENT		Docket Number: **12961/46101**
Application Number: **09/700,094**	Filing Date: **January 02, 2001**	
Patent Number: **6,713,464**	Issue Date: **March 30, 2004**	
Invention Title: **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s): **Claus MEESE et al.**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

SCHWARZ PHARMA AG, as assignee of the entire interest of the above-identified patent by virtue of executed assignments as indicated below, hereby revokes all powers of attorney previously given and appoints Bradford Paul Schmidt, Reg. No. 42,128, and the practitioners associated with Kenyon & Kenyon's customer number:

26646

to prosecute and transact all business in the Patent and Trademark Office connected therewith.

SCHWARZ PHARMA AG, is the assignee of the entire right, title and interest in U.S. Patent Application Serial No. 09/700,094 filed on January 02, 2001, now U.S. Patent No. 6,713,464 issued on March 30, 2004 by virtue of the following assignment of title from the inventor(s) to the current assignee as shown below:

1. From: Claus Meese, and

   From: Bengt Sparf

   To: Schwarz Pharma AG

The document was recorded on January 11, 2001 in the United States Patent and Trademark Office at Reel 011443, Frame 0478.

Please send all correspondence and direct telephone calls to:

Jeffrey Ginsberg, Esq.
Kenyon & Kenyon
One Broadway
New York, NY 10004
Customer No: 26646

The undersigned are authorized to act on behalf of the assignee:

Date: **August 22, 2005**

SCHWARZ PHARMA AG

By: Klaus Ve

Name: **Klaus Veltinger, MD**

Title: **Executive Board Member, Schwarz Pharma AG**

SCHWARZ PHARMA AG

Date:_____

By: _____

Name:_____

Title:_____

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		
REVOCATION OF PRIOR POWER OF ATTORNEY and APPOINTMENT OF NEW POWER OF ATTORNEY BY ASSIGNEE and 3.73(b) STATEMENT		Docket Number: **12961/46101**
Application Number: **09/700,094**	Filing Date: **January 02, 2001**	
Patent Number: **6,713,464**	Issue Date: **March 30, 2004**	
Invention Title: **NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES**		Inventor(s): **Claus MEESE et al.**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

SCHWARZ PHARMA AG, as assignee of the entire interest of the above-identified patent by virtue of executed assignments as indicated below, hereby revokes all powers of attorney previously given and appoints Bradford Paul Schmidt, Reg. No. 42,128, and the practitioners associated with Kenyon & Kenyon's customer number:

26646

to prosecute and transact all business in the Patent and Trademark Office connected therewith.

SCHWARZ PHARMA AG, is the assignee of the entire right, title and interest in U.S. Patent Application Serial No. 09/700,094 filed on January 02, 2001, now U.S. Patent No. 6,713,464 issued on March 30, 2004 by virtue of the following assignment of title from the inventor(s) to the current assignee as shown below:

1. From: Claus Meese, and

   From: Bengt Sparf

   To: Schwarz Pharma AG

The document was recorded on January 11, 2001 in the United States Patent and Trademark Office at Reel 011443, Frame 0478.

Please send all correspondence and direct telephone calls to:

Jeffrey Ginsberg, Esq.
Kenyon & Kenyon
One Broadway
New York, NY 10004
Customer No: 26646

The undersigned are authorized to act on behalf of the assignee:

SCHWARZ PHARMA AG

Date: **August 22, 2005**

By: _____

Name: **Klaus Veitinger, MD**

Title: **Executive Board Member, Schwarz Pharma AG**

SCHWARZ PHARMA AG

Date: **August 24, 2005**

By: _____

Name: **Detlef Thielgen**

Title: **CFO and Member of the Executive Board, Schwarz Pharma AG**

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO /TITLE
09/700,094	01/02/2001	Claus Meese	12961/46101

CONFIRMATION NO. 1408

26646
KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

OC000000018227342

Date Mailed: 03/08/2006

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/01/2005.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

TIMOTHY M WILLIAMS
OIPE (703) 308-9010

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UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY DOCKET NO /TITLE
09/700,094	01/02/2001	Claus Meese	12961/46101

CONFIRMATION NO. 1408

21874
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

OC000000018227333

Date Mailed: 03/08/2006

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 09/01/2005.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

TIMOTHY M WILLIAMS
OIPE (703) 308-9010

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Family 1/1

71 record(s) per family, collapsed by 45 record(s)

Record 1/45 EP957073A1 Novel derivatives of 3,3-diphenylpropylamines | 3,3-Diphenylpropylaminderivate | Dérivés de 3,3-diphénylpropylamines

Title: Novel derivatives of 3,3-diphenylpropylamines | 3,3-Diphenylpropylaminderivate | Dérivés de 3,3-diphénylpropylamines

Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome

Priority Number: EP1998108608A

Priority Date: 1998-05-12

Application Number: EP1998108608A

Application Date: 1998-05-12

Publication Date: 1999-11-17

IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARMA AG,40789 Monheim,DE,01049371

JP F Terms:

JP FI Codes:

Assignee - Original: SCHWARZ PHARMA AG

Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly the invention concerns to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly the invention concerns to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions. <IMAGE>

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2000-07-26	AXX	+
Description: PAYMENT OF EXTENSION FEES SI PAYMENT 19980512		
2000-07-26	AKX	+
Description: PAYMENT OF DESIGNATION FEES AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT		
2000-06-21	18W	-
Description: WITHDRAWN		
1999-11-17	AX	+
Description: EXTENSION OR VALIDATION OF THE EUROPEAN PATENT TO AL; LT; LV; MK; RO; SI PAYMENT 19980512		
1999-11-17	AK	+
Description: DESIGNATED CONTRACTING STATES: EP 0957073 A1 AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT		
1999-11-17	17P	+
Description: REQUEST FOR EXAMINATION FILED 1998-05-12		

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status: RJ-WDRAW 2000-04-17 2000 Withdrawal | EX-RQ 1998-05-12 1998 Request for examination

Front Page Drawing:

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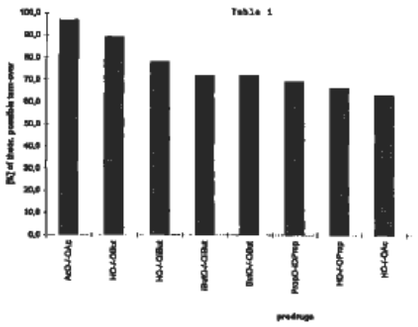
Table 1



Record 2/45 WO1999058478A1 NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES | NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES | NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: WO1999EP3212A
Application Date: 1999-05-11
Publication Date: 1999-11-18
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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IPC Class Table - DWPI:

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Assignee/Applicant: SCHWARZ PHARMA AG,DE
JP F Terms:
JP FI Codes:
Assignee - Original: SCHWARZ PHARMA AG
Any CPC Table:

Type	Invention	Additional	Version	Office
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Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
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ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

L'invention concerne de nouveaux dérivés de 3,3-diphénylpropylamines, des procédés permettant de les préparer, des compositions pharmaceutiques contenant ces nouveaux composés et l'utilisation de ces composés pour la préparation de médicaments. L'invention concerne plus particulièrement de nouveaux précurseurs d'agents anti-muscariniques qui ont des propriétés pharmacocinétiques supérieures à celles des médicaments existants tels que l'oxybutynine et la toltérodine, un procédé de préparation de ces précurseurs, des compositions pharmaceutiques les contenant et un procédé d'utilisation de ces composés, ainsi que des compositions destinées au traitement de l'incontinence urinaire, de l'hyperactivité gastro-intestinale (syndrome du côlon irritable) et d'autres pathologies affectant la contractilité des muscles lisses.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
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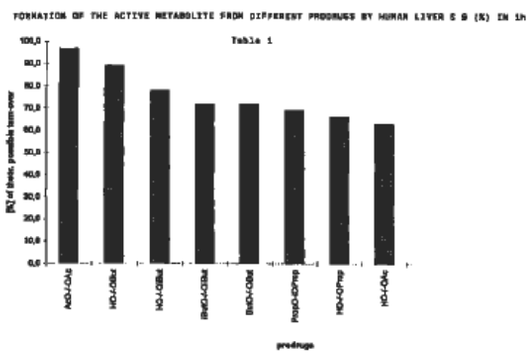
Description: WIPO INFORMATION: GRANT IN NATIONAL OFFICE CZ PV2000-3774		
2006-04-04	WWG	+
Description: WIPO INFORMATION: GRANT IN NATIONAL OFFICE KR 1020007012653		
2006-01-16	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE CZ PV2006-29		
2002-09-12	WWG	+

Description: WIPO INFORMATION: GRANT IN NATIONAL OFFICE AU 41412/99		
2002-07-03	WWG	+
Description: WIPO INFORMATION: GRANT IN NATIONAL OFFICE EP 1999924929		
2001-11-12	NENP	-
Description: NON-ENTRY INTO THE NATIONAL PHASE IN: CA		
2001-08-30	WWP	+
Description: WIPO INFORMATION: PUBLISHED IN NATIONAL OFFICE KR 1020007012653		
2001-03-15	REG	-
Description: REFERENCE TO NATIONAL CODE DE 8642 IMPACT ABOLISHED FOR DE - I.E. PCT APPL. NOT ENT. GERMAN PHASE		
2001-03-14	WWP	+
Description: WIPO INFORMATION: PUBLISHED IN NATIONAL OFFICE CZ PV2000-3774		
2001-02-28	WWP	+
Description: WIPO INFORMATION: PUBLISHED IN NATIONAL OFFICE EP 1999924929		
2001-01-02	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE US 09700094		
2000-11-11	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE KR 1020007012653		
2000-11-10	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE MX PA/a/2000/011096		
2000-11-03	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE AU 41412/99		
2000-10-19	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE EP 1999924929		
2000-10-18	WWE	+

Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE IL 139110		
2000-10-17	ENP	-
Description: ENTRY INTO THE NATIONAL PHASE IN: CA 2328920 A		
2000-10-17	ENP	-
Description: ENTRY INTO THE NATIONAL PHASE IN: CA 2328920		
2000-10-13	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE SK 15472000		
2000-10-13	ENP	-
Description: ENTRY INTO THE NATIONAL PHASE IN: SK 15472000 A		
2000-10-12	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE NZ 507487		
2000-10-11	WWE	+
Description: WIPO INFORMATION: ENTRY INTO NATIONAL PHASE CZ PV2000-3774		
2000-01-12	121	-
Description: EP: THE EPO HAS BEEN INFORMED BY WIPO THAT EP WAS DESIGNATED IN THIS APPLICATION		
1999-12-16	DFPE	-
Description: REQUEST FOR PRELIMINARY EXAMINATION FILED PRIOR TO EXPIRATION OF 19TH MONTH FROM PRIORITY DATE (PCT APPLICATION FILED BEFORE 20040101)		
1999-11-18	AL	+
Description: DESIGNATED COUNTRIES FOR REGIONAL PATENTS WO 9958478 A1 GH; GM; KE; LS; MW; SD; SL; SZ; UG; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM; AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; GW; ML; MR; NE; SN; TD; TG		
1999-11-18	AK	+
Description: DESIGNATED STATES WO 9958478 A1 AE; AL; AM; AT; AU; AZ; BA; BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GD; GE; GH; GM; HR; HU; ID; IL; IN; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; US; UZ; VN; YU; ZA; ZW		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 3/45 AU199941412A Novel derivatives of 3,3-diphenylpropylamines

Title: Novel derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: AU199941412D
Application Date: 1999-05-11
Publication Date: 1999-11-29
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222
A61K0031225	A	A61	A61K	A61K0031	A61K0031225
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K003124	A	A61	A61K	A61K0031	A61K003124

A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
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C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

Language of Publication: EN

INPADOC Legal Status Table:

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

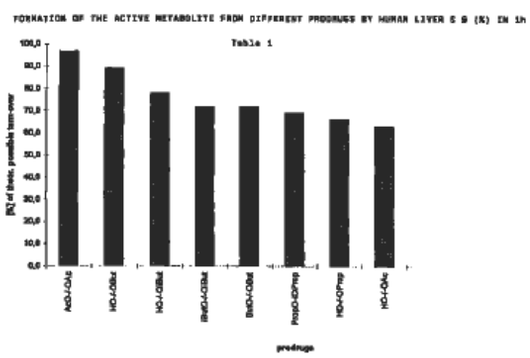
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 4/45 BR199910406A Derivados de 3,3-difenilpropilaminas

Title: Derivados de 3,3-difenilpropilaminas
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: BR199910406A
Application Date: 1999-05-11
Publication Date: 2001-01-09
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
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A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K003124	A	A61	A61K	A61K0031	A61K003124

A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
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A61K000970	A	A61	A61K	A61K0009	A61K000970
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A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
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C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

Language of Publication: PT

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2012-08-28	B07D	-
Description: TECHNICAL EXAMINATION (OPINION) RELATED TO ARTICLE 229 OF INDUSTRIAL PROPERTY LAW		
2011-05-17	B15K	-
Description: OTHERS CONCERNING APPLICATIONS: ALTERATION OF CLASSIFICATION PARA:INT.CI.C07C 1/00, C07C 217/62, C07C 217/48, C07C 219/28, C07C 219/22, C07D 207/06, C07D 295/06, C07C 271/08, C07F 7/18, C07C 307/02, A61K 31/135, A61K 31/325, A61K 31/40, A61K 31/435, A61P 13/00.		
2011-05-17	B06A	-
Description: NOTIFICATION TO APPLICANT TO REPLY TO THE REPORT FOR NON-PATENTIABILITY OR INADEQUACY OF THE APPLCATION ACCORDING ART. 36 INDUSTRIAL PATENT LAW		
2008-10-28	B06G	-
Description: TECHNICAL AND FORMAL REQUIREMENTS: OTHER REQUIREMENTS ATRAVES DA PETICAO NO 043712 DE 06/09/2001, O REQUERENTE SOLOCITOU O EXAME DO PRESENTE E EFETUOU ARETRIBUICAO EQUIVALENTE A 27 REIVINDICACOES. NO ENTANTO, EM PETICAO NO 042028 DE 29/08/2001 FOI APRESENTADO UM NOVO QUADRO REIVINDICATORIO CONSTANDO 28 REIVINDICACOES. DESSE MODO, A FIM DE DAR CONTINUIDADE AO AXAME DO PEDIDO O REQUERENTE DEVERA COMPLEMENTAR A RETRIBUICAO AQUIVALENTE A 1 REIVINDICACAO EXEDENTE.		

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

Litigation (US):

Opposition (EP):

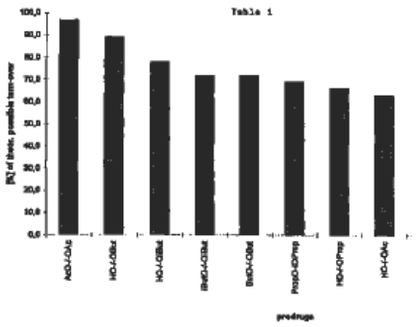
License (EP):

EPO Procedural Status:

Front Page Drawing:

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



Record 5/45 ZA200005728A Novel derivatives of 3,3-diphenylpropylamines.

Title: Novel derivatives of 3,3-diphenylpropylamines.
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: ZA20005728A
Application Date: 2000-10-17
Publication Date: 2001-03-05
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
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A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
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A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
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C07D032110	C	C07	C07D	C07D0321	C07D032110
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C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

Language of Publication: EN

INPADOC Legal Status Table:

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

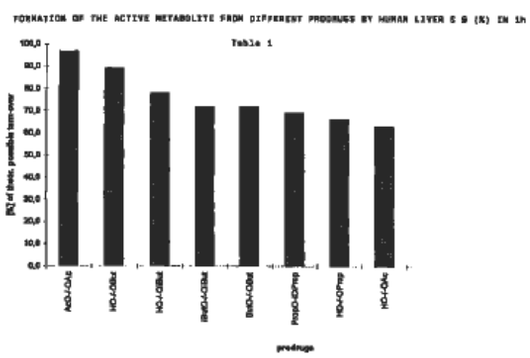
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 6/45 IL139110D0 NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: IL139110A
Application Date: 1999-05-11
Publication Date: 2001-11-25
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
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A61K0031435	A	A61	A61K	A61K0031	A61K0031435
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A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

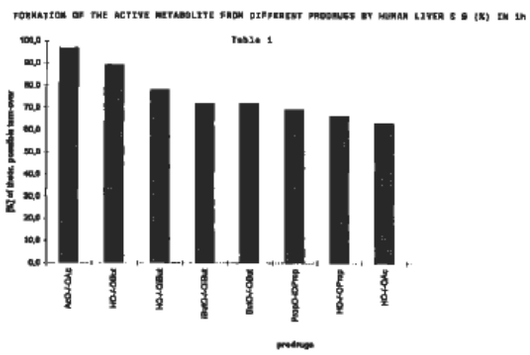
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:
ECLA:
Abstract:
Language of Publication: EN
INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2013-05-30	KB	+
Description: PATENTS RENEWED		
2010-12-30	EXTF	+
Description: APPLICATION FOR PATENT EXTENSION FILED		
2009-11-18	KB	+
Description: PATENTS RENEWED		
2009-07-20	EXTF	+
Description: APPLICATION FOR PATENT EXTENSION FILED		
2005-09-25	KB	+
Description: PATENTS RENEWED		
2005-07-25	FF	+
Description: PATENTS GRANTED		

Post-Issuance (US):

Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 7/45 TR200003319T2 3,3-Difenilpropilaminlerin yeni türevleri

Title: 3,3-Difenilpropilaminlerin yeni türevleri
Title - DWPI:
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: TR20003319T
Application Date: 1999-05-11
Publication Date: 2001-12-21
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: TR
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 8/45 AU748057B2 Novel derivatives of 3,3-diphenylpropylamines

Title: Novel derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: AU199941412A
Application Date: 1999-05-11
Publication Date: 2002-05-30
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
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A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
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C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
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A61K0031137	A	A61	A61K	A61K0031	A61K0031137
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Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2002-09-26	FGA	+
Description: LETTERS PATENT SEALED OR GRANTED (STANDARD PATENT)		

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

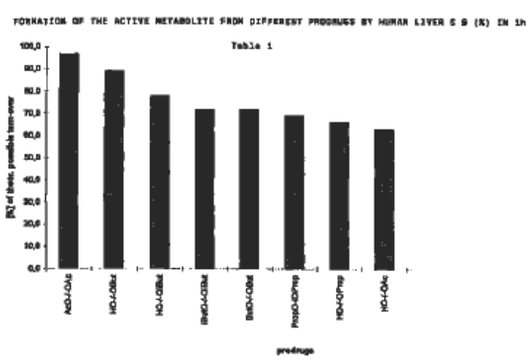
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 9/45 MX2000PA011096A NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES. | NUEVOS DERIVADOS DE 3,3 -DIFENILPROPILAMINAS.

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES. | NUEVOS DERIVADOS DE 3,3 -DIFENILPROPILAMINAS.
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: MX2000PA11096A
Application Date: 2000-11-10
Publication Date: 2002-06-04
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
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A61K0031235	A	A61	A61K	A61K0031	A61K0031235
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A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
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C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:
ECLA: C07C021748 | C07C021762 | C07C021928 | C07C027144 | C07C027152 | C07C030702
Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.
Language of Publication: ES
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 10/45 EP1077912B1 NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES | 3,3-DIPHENYLPROPYLAMINDERIVATE | NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES | 3,3-DIPHENYLPROPYLAMINDERIVATE | NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: EP1999924929A
Application Date: 1999-05-11
Publication Date: 2002-07-03
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C027144	C	C07	C07C	C07C0271	C07C027144
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARMA AG,D 40789 Monheim/Rhld.,DE,01049370
JP F Terms:
JP FI Codes:
Assignee - Original: SCHWARZ PHARMA AG
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

L'invention concerne de nouveaux dérivés de 3,3-diphénylpropylamines, des procédés permettant de les préparer, des compositions pharmaceutiques contenant ces nouveaux composés et l'utilisation de ces composés pour la préparation de médicaments. L'invention concerne plus particulièrement de nouveaux précurseurs d'agents anti-muscariniques qui ont des propriétés pharmacocinétiques supérieures à celles des médicaments existants tels que l'oxybutynine et la toltérodine, un procédé de préparation de ces précurseurs, des compositions pharmaceutiques les contenant et un procédé d'utilisation de ces composés, ainsi que des compositions destinées au traitement de l'incontinence urinaire, de l'hyperactivité gastro-intestinale (syndrome du côlon irritable) et d'autres pathologies affectant la contractilité des muscles lisses.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2013-08-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2013-08-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2013-08-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		

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Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
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Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE PT		
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Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2012-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2012-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2012-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2012-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FR		
2012-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE SE		

2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		
2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE MC		
2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IE		
2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CH		
2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE LU		
2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DK		
2012-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DE		
2011-12-30	REG	-
Description: REFERENCE TO A NATIONAL CODE CH SPCG SUPPLEMENTARY PROTECTION CERTIFICATE GRANTED PRODUCT NAME: FESOTERODIN; REGISTRATION NUMBER/DATE: SWISSMEDIC 58743 18.12.2008		
2011-11-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CY		
2011-11-15	REG	-
Description: REFERENCE TO A NATIONAL CODE CH PFA NAME/FIRM CHANGED UCB PHARMA GMBH SCHWARZ PHARMA AG#ALFRED-NOBEL-STRASSE 10#D-40789 MONHEIM/RHLD. (DE) -TRANSFER TO- UCB PHARMA GMBH#ALFRED-NOBEL-STRASSE 10#40789 MONHEIM (DE)		
2011-11-15	REG	-
Description: REFERENCE TO A NATIONAL CODE CH SPCF SUPPLEMENTARY PROTECTION CERTIFICATE FILED PRODUCT NAME: FESOTERODIN; REGISTRATION NUMBER/DATE: SWISSMEDIC 58743 18.12.2008		
2011-10-31	REG	-

Description: REFERENCE TO A NATIONAL CODE CH PK CORRECTION GESTUETZT AUF DAS AM 23.04.2010 EINGEREICHTE WIEDEREINSETZUNGSGESUCH AUF GRUND VON ART. 47 PATG, IST AM 25.10.2011 DIE WIEDEREINSETZUNG IN DIE ESZ-FRIS		
2011-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DE		
2011-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IT		
2011-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2011-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		
2011-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2011-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE AT		
2011-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DK		
2011-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FR		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE ES		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CH		

2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE LU		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE MC		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE SE		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE PT		
2011-07-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IE		
2011-05-27	REG	-
Description: REFERENCE TO A NATIONAL CODE FI SPCG SUPPLEMENTARY PROTECTION CERTIFICATE SPC GRANTED		
2010-12-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2010-11-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CY		
2010-11-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE SE		
2010-10-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CH		
2010-10-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		

2010-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE AT		
2010-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DE		
2010-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		
2010-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IT		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE PT		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE MC		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE LU		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IE		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FR		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DK		
2010-07-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE ES		

2010-06-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2010-02-10	REG	-
Description: REFERENCE TO A NATIONAL CODE GB CTFG CERTIFICATE GRANTED PRODUCT NAME: FESOTERODINE AND ITS SALTS WITH PHYSIOLOGICALLY ACCEPTABLE ACIDS, INCLUDING FUMARIC ACID; REGISTERED: UK EU/1/07/386/001 20070420; UK EU/1/07/386/002 20070420; UK EU/1/07/386/003 20070420; UK EU/1/07/386/004 20070420; UK EU/1/07/386/005 20070420; UK EU/1/07/386/006 20070420; UK EU/1/07/386/007 20070420; UK EU/1/07/386/008 20070420; UK EU/1/07/386/009 20070420; UK EU/1/07/386/010 20070420 2010-01-14		
2009-12-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CY		
2009-11-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2009-11-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2009-10-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CH		
2009-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE AT		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE SE		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE PT		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE LU		
2009-08-31	PGFP	+

Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IT		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FR		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2009-08-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DE		
2009-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DK		
2009-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE ES		
2009-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IE		
2009-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE MC		
2009-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		
2009-05-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2009-03-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2008-12-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2008-10-31	PGFP	+

Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE SE		
2008-10-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IE		
2008-10-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		
2008-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE MC		
2008-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CY		
2008-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2008-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE PT		
2008-09-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IT		
2008-08-29	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE AT		
2008-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CH		
2008-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE LU		
2008-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DK		
2008-07-31	PGFP	+

Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DE		
2008-07-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE ES		
2008-06-11	REG	-
Description: REFERENCE TO A NATIONAL CODE IE SPCG SUPPLEMENTARY PROTECTION CERTIFICATE GRANTED SPC037/2007: 20080507, EXPIRES: 20220419		
2008-05-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2008-05-09	REG	-
Description: REFERENCE TO A NATIONAL CODE FR CY SUPPLEMENTARY CERTIFICATE OF PROTECTION GRANTED (EEC REGULATION OF 18 JUNE 1992) PRODUCT NAME: FESOTERODINE ET SES SELS AVEC DES ACIDES PHYSIOLOGIQUEMENT ACCEPTABLES NOTAMMENT L ACIDE FUMARIQUE; REGISTRATION NO/DATE IN FRANCE: EU/1/07/386/001 DU 20070420; REGISTRATION NO/DATE AT EEC: EU/1/07/386/001 DU 20070420		
2008-04-30	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FR		
2008-03-18	REG	-
Description: REFERENCE TO A NATIONAL CODE SE SPCG GRANTED SUPPLEMENTARY PROTECTION CERTIFICATE 0790047-5		
2008-03-18	REG	-
Description: REFERENCE TO A NATIONAL CODE SE SPCG GRANTED SUPPLEMENTARY PROTECTION CERTIFICATE		
2008-02-15	REG	-
Description: REFERENCE TO A NATIONAL CODE CH PFA NAME/FIRM CHANGED SCHWARZ PHARMA AG SCHWARZ PHARMA AG#ALFRED-NOBEL-STRASSE 10#D-40789 MONHEIM/RHLD. (DE) -TRANSFER TO- SCHWARZ PHARMA AG#ALFRED-NOBEL-STRASSE 10#D-40789 MONHEIM/RHLD. (DE)		
2008-01-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2008-01-11	REG	-
Description: REFERENCE TO A NATIONAL CODE FR CP SUPPLEMENTARY CERTIFICATE OF PROTECTION		

FILED		
2008-01-02	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IT		
2007-11-24	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2007-11-16	REG	-
Description: REFERENCE TO A NATIONAL CODE FR CR SUPPLEMENTARY CERTIFICATE OF PROTECTION LAID OPEN TO THE PUBLIC (EEC REGULATION OF 18 JUNE 1992) PRODUCT NAME: FESOTERODINE ET SES SELS AVEC DES ACIDES PHYSIOLOGIQUEMENT ACCEPTABLES NOTAMMENT L ACIDE FUMARIQUE; REGISTRATION NO/DATE IN FRANCE: EU/1/07/386/001 DU 20070420; REGISTRATION NO/DATE AT EEC: EU/1/07/386/001 DU 20070420		
2007-11-14	REG	-
Description: REFERENCE TO A NATIONAL CODE LU CCP SUPPLEMENTARY PROTECTION CERTIFICATE 91365, EXPIRES: 20220420		
2007-11-12	REG	-
Description: REFERENCE TO A NATIONAL CODE DK CTFF SUPPLEMENTARY PROTECTION CERTIFICATE FILED		
2007-11-06	REG	-
Description: REFERENCE TO A NATIONAL CODE SE SPCF APPLICATION FOR SUPPLEMENTARY PROTECTION CERTIFICATE PRODUCT NAME: FESOTERODIN OCH DESS SALTER MED FYSIKALISKT GODTAGBARA SYROR,; NAT REG. NO/DATE: EG EU/1/07/386/001 20070420; FIRST REG.: EG EU/1/07/386/001 20070420		
2007-11-06	REG	-
Description: REFERENCE TO A NATIONAL CODE SE SPCF APPLICATION FOR SUPPLEMENTARY PROTECTION CERTIFICATE PRODUCT NAME; FESOTERODIN OCH DESS SALTER MED FYSIKALISKT GODTAGBARA SYROR, INKLUDERANDE FUMARSYRA REGISTRATION NO/DATE: EU/1/07/386/001 / 20071106		
2007-11-06	REG	-
Description: REFERENCE TO A NATIONAL CODE SE SPCF APPLICATION FOR SUPPLEMENTARY PROTECTION CERTIFICATE 0790047-5, 20070420		
2007-11-01	REG	-
Description: REFERENCE TO A NATIONAL CODE NL AC1 APPLICATION FOR A SUPPLEMENTARY PROTECTION CERTIFICATE		

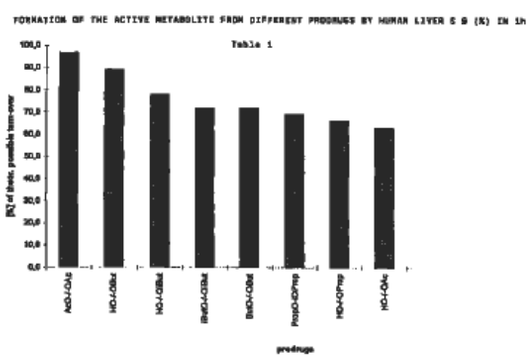
2007-10-31	REG	-
Description: REFERENCE TO A NATIONAL CODE GB CTFF CERTIFICATE FILED SPC/GB07/053: 20071003		
2007-10-18	REG	-
Description: REFERENCE TO A NATIONAL CODE FI SPCF SUPPLEMENTARY PROTECTION CERTIFICATE APPLICATION FILED		
2007-10-17	REG	-
Description: REFERENCE TO A NATIONAL CODE IE SPCF REQUEST FOR GRANT OF SUPPLEMENTARY PROTECTION CERTIFICATE SPC037/2007: 20070914		
2007-06-21	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE ES		
2007-05-24	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE LU		
2007-05-16	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CH		
2007-05-15	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DK		
2007-05-14	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FI		
2007-05-14	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IE		
2007-05-11	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE AT		
2007-05-09	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE PT		
2007-05-08	PGFP	+

Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE SE		
2007-05-03	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE NL		
2007-05-03	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE DE		
2007-04-26	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE MC		
2007-04-19	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE CY		
2006-07-12	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE BE		
2006-05-31	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE IT		
2006-05-15	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE FR		
2006-05-10	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GB		
2006-04-13	PGFP	+
Description: POSTGRANT: ANNUAL FEES PAID TO NATIONAL OFFICE GR		
2003-06-25	26N	+
Description: NO OPPOSITION FILED 2003-04-04		
2003-02-16	REG	-
Description: REFERENCE TO A NATIONAL CODE ES FG2A DEFINITIVE PROTECTION		
2002-12-30	LTIE	-

Description: LT: INVALIDATION OF EUROPEAN PATENT OR PATENT EXTENSION 2002-07-03		
2002-12-06	ET	+
Description: FR: TRANSLATION FILED		
2002-11-29	REG	-
Description: REFERENCE TO A NATIONAL CODE PT SC4A TRANSLATION IS AVAILABLE AVAILABILITY OF NATIONAL TRANSLATION 2002-10-02		
2002-10-28	REG	-
Description: REFERENCE TO A NATIONAL CODE DK T3 TRANSLATION OF EP PATENT		
2002-10-15	REG	-
Description: REFERENCE TO A NATIONAL CODE CH NV NEW AGENT		
2002-08-08	REF	-
Description: CORRESPONDS TO: DE 69902037		
2002-07-24	REG	-
Description: REFERENCE TO A NATIONAL CODE IE FG4D EUROPEAN PATENTS GRANTED DESIGNATING IRELAND		
2002-07-15	REG	-
Description: REFERENCE TO A NATIONAL CODE CH EP ENTRY IN THE NATIONAL PHASE		
2002-07-03	REF	-
Description: CORRESPONDS TO: AT 220056 T		
2002-07-03	AX	+
Description: EXTENSION OR VALIDATION OF THE EUROPEAN PATENT TO AL PAYMENT 20001019; LT PAYMENT 20001019; LV PAYMENT 20001019; MK PAYMENT 20001019; RO PAYMENT 20001019; SI PAYMENT 20001019		
2002-07-03	AK	+
Description: DESIGNATED CONTRACTING STATES: EP 1077912 B1 AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE		
2002-01-16	17Q	+
Description: FIRST EXAMINATION REPORT 2001-12-04		

2001-02-28	AX	+
Description: EXTENSION OR VALIDATION OF THE EUROPEAN PATENT TO AL PAYMENT 20001019; LT PAYMENT 20001019; LV PAYMENT 20001019; MK PAYMENT 20001019; RO PAYMENT 20001019; SI PAYMENT 20001019		
2001-02-28	AK	+
Description: DESIGNATED CONTRACTING STATES: EP 1077912 A1 AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE		
2001-02-28	17P	+
Description: REQUEST FOR EXAMINATION FILED 2000-10-19		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status: EX-RQ 2000-10-19 2000 Request for examination | EX-REPORT 2001-12-04 2001 Dispatch of 1st examination report
Front Page Drawing:



Record 11/45 AT220056T 3,3-DIPHENYLPROPYLAMINDERIVATE

Title: 3,3-DIPHENYLPROPYLAMINDERIVATE
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: AT1999924929T
Application Date: 1999-05-11
Publication Date: 2002-07-15
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: XX
INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2008-05-15	EEZF	+
Description: GRANT FOR A CERTIFICATE OF PROTECTION (E-SERIES) SZ 47/2007, 20071005, EXPIRES:20220420		
2008-01-15	ESZA	+
Description: APPLICATION FILED FOR A CERTIFICATE OF PROTECTION (E-SERIES) SZ 47/2007, 20071005		
2002-12-15	UEP	+
Description: PUBLICATION OF TRANSLATION OF EUROPEAN PATENT SPECIFICATION		

Post-Issuance (US):

Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 12/45 DK1077912T3 Hidtil ukendte derivater af 3,3-diphenylpropylaminer

Title: Hidtil ukendte derivater af 3,3-diphenylpropylaminer
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: DK1999924929T
Application Date: 1999-05-11
Publication Date: 2002-10-28
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: DA
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 13/45 EP1254890A1 Derivatives of 3,3-diphenylpropylamines | 3,3-Diphenylpropylaminderivate | Dérivés de 3,3-diphénylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines | 3,3-Diphenylpropylaminderivate | Dérivés de 3,3-diphénylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | EP1999924929A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: EP200213481A
Application Date: 1999-05-11
Publication Date: 2002-11-06
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144

C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
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A61K0031222	A	A61	A61K	A61K0031	A61K0031222
A61K0031225	A	A61	A61K	A61K0031	A61K0031225
A61K0031235	A	A61	A61K	A61K0031	A61K0031235

A61K003124	A	A61	A61K	A61K0031	A61K003124
A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
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A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900

C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
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C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARMA AG,D 40789 Monheim/Rhld.,DE,01049370
JP F Terms:
JP FI Codes:
Assignee - Original: SCHWARZ PHARMA AG
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3- diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

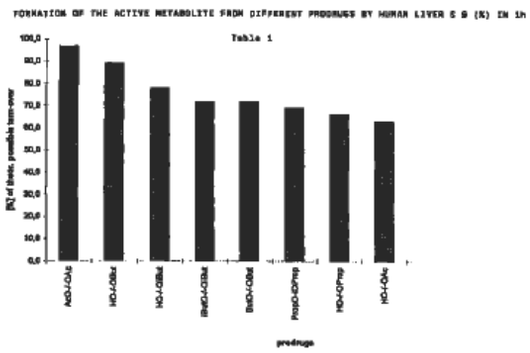
Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2004-03-31	18D	-
Description: DEEMED TO BE WITHDRAWN 2003-05-07		
2003-08-28	REG	-
Description: REFERENCE TO A NATIONAL CODE DE 8566 DESIGNATED COUNTRY DE NOT LONGER VALID		
2003-07-23	AKX	+
Description: PAYMENT OF DESIGNATION FEES		
2002-11-06	AX	+
Description: EXTENSION OR VALIDATION OF THE EUROPEAN PATENT TO AL; LT; LV; MK; RO; SI		
2002-11-06	AK	+
Description: DESIGNATED CONTRACTING STATES: EP 1254890 A1 AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE		
2002-11-06	AC	-

Description: DIVISIONAL APPLICATION (ART. 76) OF: EP 1077912

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status: RJ-DWDRAW 2003-05-07 2003 Deemed to be withdrawn
Front Page Drawing:



Record 14/45 NZ507487A 3,3-Diphenylpropylamine derivatives useful as anti muscarinic agents

Title: 3,3-Diphenylpropylamine derivatives useful as anti muscarinic agents
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: NZ507487A
Application Date: 1999-05-11
Publication Date: 2002-11-26
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
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A61K0031225	A	A61	A61K	A61K0031	A61K0031225
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A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
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A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
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A61P002100	A	A61	A61P	A61P0021	A61P002100
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A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
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C07H001518	C	C07	C07H	C07H0015	C07H001518
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

3,3-diphenylpropylamines of formulae I and VII' (as described in the specification) and their derivatives, methods for their preparation, pharmaceutical compositions containing 3,3-diphenylpropylamines. These 3,3-diphenylpropylamines can be used for preparing drugs such as antimuscarinic agents for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2012-05-25	RENW	+
Description: RENEWAL (RENEWAL FEES ACCEPTED)		
2009-05-29	RENW	+
Description: RENEWAL (RENEWAL FEES ACCEPTED)		
2006-05-26	RENW	+
Description: RENEWAL (RENEWAL FEES ACCEPTED)		
2003-10-31	RENW	+
Description: RENEWAL (RENEWAL FEES ACCEPTED)		
2003-03-28	PSEA	+
Description: PATENT SEALED		

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

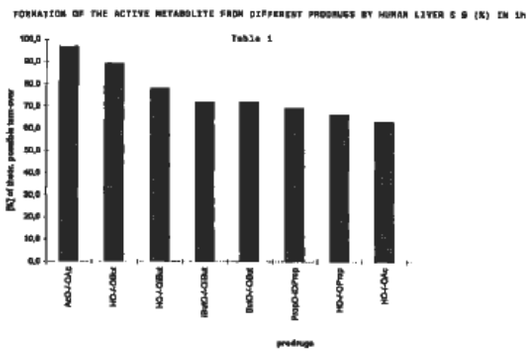
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 15/45 PT1077912E NOVOS DERIVADOS DE 3,3-DIFENILPROPILAMINAS

Title: NOVOS DERIVADOS DE 3,3-DIFENILPROPILAMINAS
Title - DWPI:
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: PT924929T
Application Date: 1999-05-11
Publication Date: 2002-11-29
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: PT
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 16/45 DE69902037T2 3,3-DIPHENYLPROPYLAMINDERIVATE

Title: 3,3-DIPHENYLPROPYLAMINDERIVATE
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: DE69902037A
Application Date: 1999-05-11
Publication Date: 2003-02-06
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: Schwarz Pharma AG
JP F Terms:
JP FI Codes:
Assignee - Original: Schwarz Pharma AG
Any CPC Table:

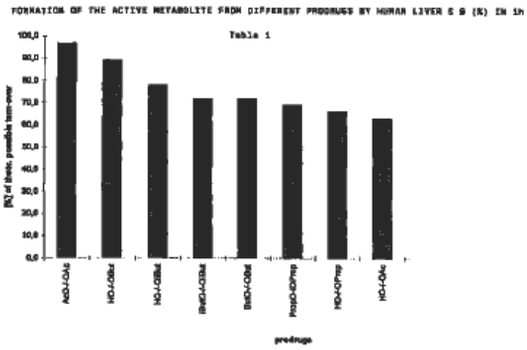
Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

L'invention concerne de nouveaux dérivés de 3,3-diphénylpropylamines, des procédés permettant de les préparer, des compositions pharmaceutiques contenant ces nouveaux composés et l'utilisation de ces composés pour la préparation de médicaments. L'invention concerne plus particulièrement de nouveaux précurseurs d'agents anti-muscariniques qui ont des propriétés pharmacocinétiques supérieures à celles des médicaments existants tels que l'oxybutynine et la toltérodine, un procédé de préparation de ces précurseurs, des compositions pharmaceutiques les contenant et un procédé d'utilisation de ces composés, ainsi que des compositions destinées au traitement de l'incontinence urinaire, de l'hyperactivité gastro-intestinale (syndrome du côlon irritable) et d'autres pathologies affectant la contractilité des muscles lisses.
Language of Publication: DE

INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 17/45 ES2181443T3 NUEVOS DERIVADOS DE 3,3-DIFENILPROPILAMINAS.

Title: NUEVOS DERIVADOS DE 3,3-DIFENILPROPILAMINAS.
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: ES1999924929T
Application Date: 1999-05-11
Publication Date: 2003-02-16
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
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A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
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A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
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A61K0031315	A	A61	A61K	A61K0031	A61K0031315
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A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
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C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
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C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

Language of Publication: ES

INPADOC Legal Status Table:

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

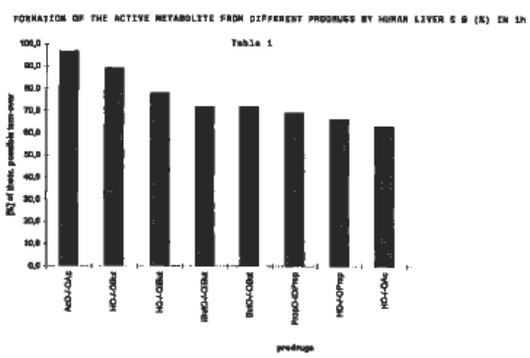
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 18/45 RU2199525C2 NOVEL DERIVATIVES OF 3,3-DIPHENYLROPYLAMINES, METHODS OF THEIR SYNTHESIS (VERSIONS) AND PHARMACEUTICAL COMPOSITION COMPRISING THEREOF

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLROPYLAMINES, METHODS OF THEIR SYNTHESIS (VERSIONS) AND PHARMACEUTICAL COMPOSITION COMPRISING THEREOF
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: RU2000125813A
Application Date: 1999-05-11
Publication Date: 2003-02-27
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
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C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108

C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

FIELD: organic chemistry, chemical technology, pharmacy. SUBSTANCE: invention describes derivatives of 3,3-diphenylpropyl-amines of the general formula (I) and where R and R1 are taken independently among hydrogen atom, C1-C6-alkyl, C3-C10-cycloalkyl, C1-C6-alkylcarbonyl, C1-C6-alkoxycarbonyl, substituted or unsubstituted benzene and others; X means tertiary amino-group; Y and Z mean independently a single bond between (CH2)n-group and carbonyl group, O, S or NH; A means hydrogen atom (1H) or deuterium (2H); n is a number from 0 to 12, and their salts with physiologically acceptable acids, their free bases. Invention relates also to methods of their synthesis, pharmaceutical compositions comprising these compounds and the use of these compounds for antimuscarine drug preparing. Invention provides preparing novel prodrugs of antimuscarine agents with good pharmacokinetic properties as compared with existing drugs, for example, oxybutynin and tolterodine. The synthesized compounds and pharmaceutical compositions comprising thereof are used for treatment of enuresis and other contractile states of smooth muscles. EFFECT: improved methods of synthesis, valuable medicinal properties of agents and composition. 30 cl, 2 dwg, 5 tbl

Language of Publication: RU

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2013-08-20	PD4A	-
Description: CORRECTION OF NAME OF PATENT OWNER		

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

Litigation (US):

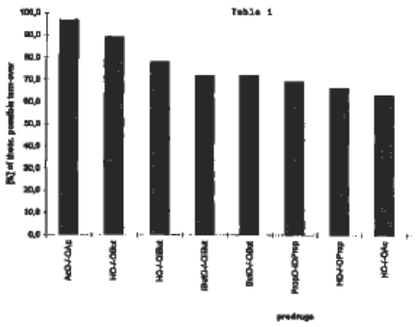
Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h



Record 19/45 US6713464B1 Derivatives of 3,3-diphenylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: US2000700094A
Application Date: 2001-01-02
Publication Date: 2004-03-30
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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Assignee/Applicant: Schwarz Pharma AG,Monheim,DE
JP F Terms:
JP FI Codes:
Assignee - Original: Schwarz Pharma AG
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2011-08-31	FPAY	+
Description: FEE PAYMENT		
2010-05-24	AS	-
Description: ASSIGNMENT UCB PHARMA GMBH, GERMANY CHANGE OF NAME; ASSIGNOR:SCHWARZ PHARMA AG; REEL/FRAME:024424/0724 2010-01-20		
2007-09-07	FPAY	+
Description: FEE PAYMENT		
2007-02-20	AS	-
Description: ASSIGNMENT PFIZER INC.,NEW YORK CONFIRMATION OF EXCLUSIVE PATENT LICENSE; ASSIGNORS:SCHWARZ PHARMA AG; SCHWARZ PHARMA LIMITED; REEL/FRAME:018942/0916 2006-04-12		

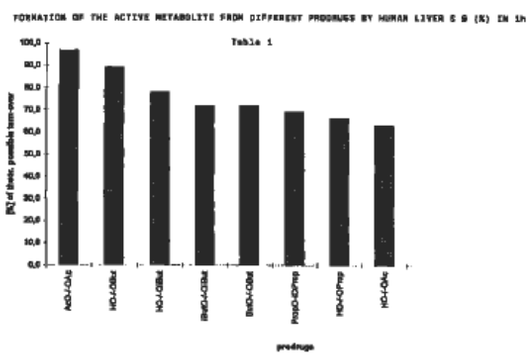
Post-Issuance (US): CORR-CERT Certificate of Correction 2005-05-31 2005 2005-06-21 2005 a Certificate of Correction was issued for this patent

Reassignment (US) Table:

Assignee	Assignor	Date Signed	Reel/Frame	Date

PFIZER INC.,NEW YORK,NY,US	SCHWARZ PHARMA AG	2006-04-12	018942/0916	2007-02-20
	SCHWARZ PHARMA LIMITED	2006-04-12		
Conveyance: CONFIRMATION OF EXCLUSIVE PATENT LICENSE				
Corresponent: CARL J. GODDARD PFIZER INC., PATENT DEPT. EASTERN POINT RD. GROTON, CT 06340				
SCHWARZ PHARMA AG,MONHEIM,DE	MEESE, CLAUS	2000-12-13	011443/0478	2001-01-11
	SPARF, BENGT	2000-12-13		
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).				
Corresponent: MCDONNELL BOEHNEN, HULBERT & BERGHOFF MICHAEL S. GREENFIELD 300 SOUTH WACKER DRIVE, SUITE 3200 CHICAGO, IL 60606				

Maintenance Status (US): CC
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 20/45 CN1207268C Novel derivatives of 3-3-diphenylpropylamines | 3, 3-diphenyl-propyl amine derivant

Title: Novel derivatives of 3-3-diphenylpropylamines | 3, 3-diphenyl-propyl amine derivant
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: CN1999806038A
Application Date: 1999-05-11
Publication Date: 2005-06-22
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C030700	C	C07	C07C	C07C0307	C07C030700
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A61P001302	A	A61	A61P	A61P0013	A61P001302
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A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
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C07C023347	C	C07	C07C	C07C0233	C07C023347

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C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
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C07D032110	C	C07	C07D	C07D0321	C07D032110
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C07C022902	C	C07	C07C	C07C0229	C07C022902
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARMA AG,US
JP F Terms:
JP FI Codes:
Assignee - Original: SCHWARZ PHARMA AG
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

This invention relates to the 3, 3-diphenyl-propyl amine of formula I and VII and with a physiologically acceptable acid salt, free base and/or racemic mixture and enantiomer. Definition of each group and symbol specification. They are applied to the muscarinic medicine in the active substance.

L'invention concerne de nouveaux dérivés de 3,3-diphénylpropylamines, des procédés permettant de les préparer, des compositions pharmaceutiques contenant ces nouveaux composés et l'utilisation de ces composés pour la préparation de médicaments. L'invention concerne plus particulièrement de nouveaux précurseurs d'agents anti-muscariniques qui ont des propriétés pharmacocinétiques supérieures à celles des médicaments existants tels que l'oxybutynine et la toltérodine, un procédé de préparation de ces précurseurs, des compositions pharmaceutiques les contenant et un procédé d'utilisation de ces composés, ainsi que des compositions destinées au traitement de l'incontinence urinaire, de l'hyperactivité gastro-intestinale (syndrome du côlon irritable) et d'autres pathologies affectant la contractilité des muscles lisses.

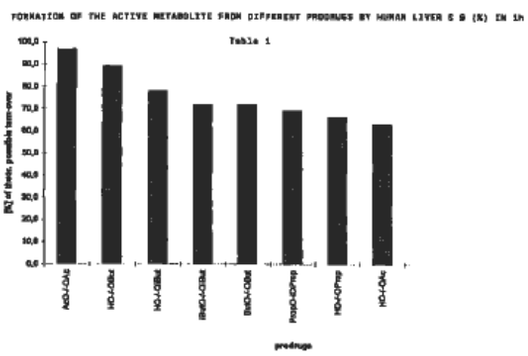
Language of Publication: ZH

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2011-05-18	C56	-
Description: CHANGE IN THE NAME OR ADDRESS OF THE PATENTEE UCB PHARMA INC. FORMER NAME: SCHWARZ PHARMA AG		
2011-05-18	C56	-
Description: CHANGE IN THE NAME OR ADDRESS OF THE PATENTEE		

2005-06-22	C14	+
Description: GRANTED		
2002-06-19	C06	+
Description: PUBLICATION		
2002-06-05	C10	-
Description: REQUEST OF EXAMINATION AS TO SUBSTANCE		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 21/45 IS2044B Nyjar afleithur af 3,3-dífenylpropylamínum

Title: Nyjar afleithur af 3,3-dífenylpropylamínum
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: IS5670A
Application Date: 2000-10-17
Publication Date: 2005-09-15
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
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C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: IS
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 22/45 HK1046269A1 Derivatives of 3,3-diphenylpropylamines.

Title: Derivatives of 3,3-diphenylpropylamines.
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: HK2002107859A
Application Date: 2002-10-30
Publication Date: 2005-09-23
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
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A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
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C07D029506	C	C07	C07D	C07D0295	C07D029506
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C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: ZH
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 23/45 CZ296605B6 3,3-Diphenylpropylamines, pharmaceutical compositions, process of their preparation and use

Title: 3,3-Diphenylpropylamines, pharmaceutical compositions, process of their preparation and use
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: CZ20003774A
Application Date: 1999-05-11
Publication Date: 2006-04-12
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144

C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
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C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
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C07C021928	C	C07	C07C	C07C0219	C07C021928
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C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
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C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

In the present invention, there are disclosed novel derivatives of 3,3-diphenylpropylamines, processes for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing medicaments. More particularly, the invention relates to novel prodrugs of anti-muscarine agents with superior pharmacokinetic properties, processes for their preparation, pharmaceutical compositions containing them, a method of using said compounds and pharmaceutical compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

Language of Publication: CS

INPADOC Legal Status Table:

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

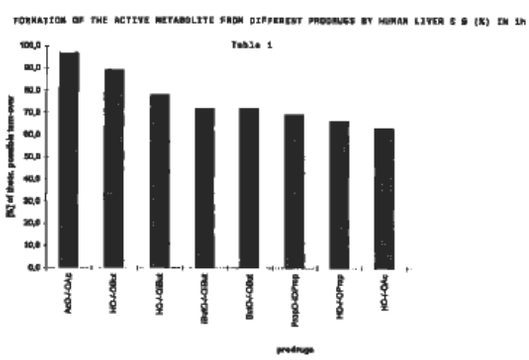
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 24/45 US7230030B2 Derivatives of 3,3-diphenylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A | US2001700094A
Priority Date: 1998-05-12 | 1999-05-11 | 2001-01-02
Application Number: US2004766263A
Application Date: 2004-01-27
Publication Date: 2007-06-12
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762

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C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C021928	C	C07	C07C	C07C0219	C07C021928
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C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
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C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
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C07C022902	C	C07	C07C	C07C0229	C07C022902
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C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: Schwarz Pharma AG,Monheim,DE
JP F Terms:
JP FI Codes:
Assignee - Original: Schwarz Pharma AG
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.
Language of Publication: EN
INPADOC Legal Status Table:

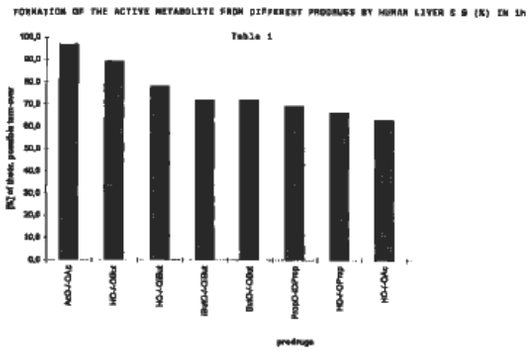
Gazette Date	Code	INPADOC Legal Status Impact
2010-11-10	FPAY	+
Description: FEE PAYMENT		
2010-05-24	AS	-
Description: ASSIGNMENT UCB PHARMA GMBH, GERMANY CHANGE OF NAME; ASSIGNOR:SCHWARZ PHARMA AG; REEL/FRAME:024424/0724 2010-01-20		

Post-Issuance (US):
Reassignment (US) Table:

Assignee	Assignor	Date Signed	Reel/Frame	Date
UCB PHARMA GMBH,MONHEIM,DE	SCHWARZ PHARMA AG	2010-01-20	024424/0724	2010-05-24

Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).
Corresponent: JEFFREY GINSBERG ONE BROADWAY KENYON & KENYON LLP NEW YORK, NY 10004

Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 25/45 JP03929702B2 The novel derivative of a 3, 3- diphenyl propyl amine

Title: The novel derivative of a 3, 3- diphenyl propyl amine
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: JP2000548284A
Application Date: 1999-05-11
Publication Date: 2007-06-13
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
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A61K003140	A	A61	A61K	A61K0031	A61K003140
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A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
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A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021922	C	C07	C07C	C07C0219	C07C021922
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C07C030702	C	C07	C07C	C07C0307	C07C030702
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IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARM AG

JP F Terms: | 4B064AE01 | 4B064CA21 | 4B064CB25 | 4B064CC03 | 4B064CD12 | 4B064DA01 | 4C022MA02 | 4C057AA18 | 4C057BB02 | 4C057DD01 | 4C057JJ20 | 4C086AA01 | 4C086AA02 | 4C086AA03 | 4C086AA04 | 4C086CA03 | 4C086EA07 | 4C086MA01 | 4C086MA02 | 4C086MA04 | 4C086MA05 | 4C086NA06 | 4C086NA11 | 4C086NA14 | 4C086NA15 | 4C086ZA66 | 4C086ZA84 | 4C086ZA94 | 4C086ZC42 | 4C201 | 4C206AA01 | 4C206AA02 | 4C206AA03 | 4C206AA04 | 4C206DB04 | 4C206DB11 | 4C206DB15 | 4C206DB16 | 4C206DB18 | 4C206DB29 | 4C206DB57 | 4C206FA51 | 4C206GA13 | 4C206GA22 | 4C206HA24 | 4C206MA01 | 4C206MA02 | 4C206MA04

| 4C206MA05 | 4C206NA06 | 4C206NA11 | 4C206NA14 | 4C206NA15 | 4C206ZA66 | 4C206ZA84 | 4C206ZA94 | 4C206ZC42 | 4H006AA01 | 4H006AA02 | 4H006AA03 | 4H006AB20 | 4H006AC13 | 4H006AC48 | 4H006AC52 | 4H006AC56 | 4H006BJ50 | 4H006BN10
JP FI Codes: | A61K0031235 | A61K0031325 | A61K0031357 | A61K0031365 | A61K00317028 | A61P000100 | A61P001300 | A61P004300-111 | C07C021306 | C07C021762 | C07C021928 | C07C027108 | C07C030702 | C07D032100 | C07H001518 | C12P001300
Assignee - Original: SCHWARZ PHARM AG
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

L'invention concerne de nouveaux dérivés de 3,3-diphénylpropylamines, des procédés permettant de les préparer, des compositions pharmaceutiques contenant ces nouveaux composés et l'utilisation de ces composés pour la préparation de médicaments. L'invention concerne plus particulièrement de nouveaux précurseurs d'agents anti-muscariniques qui ont des propriétés pharmacocinétiques supérieures à celles des médicaments existants tels que l'oxybutynine et la toltérodine, un procédé de préparation de ces précurseurs, des compositions pharmaceutiques les contenant et un procédé d'utilisation de ces composés, ainsi que des compositions destinées au traitement de l'incontinence urinaire, de l'hyperactivité gastro-intestinale (syndrome du côlon irritable) et d'autres pathologies affectant la contractilité des muscles lisses.
Language of Publication: JA
INPADOC Legal Status Table:

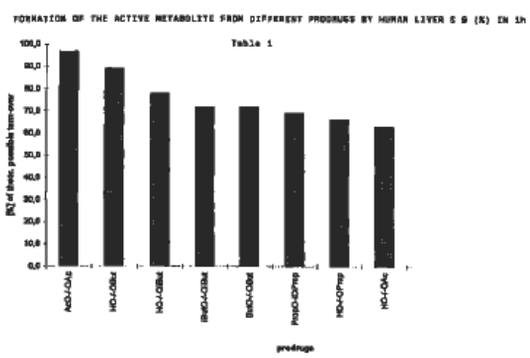
Gazette Date	Code	INPADOC Legal Status Impact
2013-06-19	R153	+
Description: GRANT OF PATENT TERM EXTENSION JAPANESE INTERMEDIATE CODE: R153		

2013-04-03	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140316		
2013-03-05	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140316		
2013-02-28	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20130316		
2012-03-06	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20130316		
2012-03-01	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20120316		
2011-04-27	R350	-
Description: WRITTEN NOTIFICATION OF REGISTRATION OF TRANSFER JAPANESE INTERMEDIATE CODE: R350		
2011-04-27	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20120316		
2011-04-19	S201	-
Description: REQUEST FOR REGISTRATION OF EXCLUSIVE LICENCE JAPANESE INTERMEDIATE CODE: R314201		
2011-04-13	RD04	-
Description: NOTIFICATION OF RESIGNATION OF POWER OF ATTORNEY JAPANESE INTERMEDIATE CODE: R3D04		
2011-04-13	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20120316		

2011-03-28	RD02	-
Description: NOTIFICATION OF ACCEPTANCE OF POWER OF ATTORNEY JAPANESE INTERMEDIATE CODE: R3D02		
2011-03-03	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20110316		
2011-02-10	R350	-
Description: WRITTEN NOTIFICATION OF REGISTRATION OF TRANSFER JAPANESE INTERMEDIATE CODE: R350		
2011-02-10	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20110316		
2011-02-02	S533	-
Description: WRITTEN REQUEST FOR REGISTRATION OF CHANGE OF NAME JAPANESE INTERMEDIATE CODE: R313533		
2011-02-02	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20110316		
2010-03-09	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20110316		
2007-03-16	R150	+
Description: CERTIFICATE OF PATENT (=GRANT) OR REGISTRATION OF UTILITY MODEL JAPANESE INTERMEDIATE CODE: R150		
2007-03-15	A61	+
Description: FIRST PAYMENT OF ANNUAL FEES (DURING GRANT PROCEDURE) JAPANESE INTERMEDIATE CODE: A61 2007-03-07		
2007-02-27	A01	+
Description: WRITTEN DECISION TO GRANT A PATENT OR TO GRANT A REGISTRATION (UTILITY MODEL) JAPANESE INTERMEDIATE CODE: A01 2007-02-26		

2007-02-21	TRDD	+
Description: DECISION OF GRANT OR REJECTION WRITTEN		
2007-01-19	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2007-01-18		
2006-12-05	A131	-
Description: NOTIFICATION OF REASONS FOR REFUSAL JAPANESE INTERMEDIATE CODE: A131 2006-12-04		
2006-10-19	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2006-10-18		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 26/45 PL195581B1 NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: PL347823A
Application Date: 1999-05-11
Publication Date: 2007-10-31
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021928	C	C07	C07C	C07C0219	C07C021928
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: PL
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 27/45 LU91365I2 Fésotérodine et ses sels avec des acides physiologiquement acceptables, y compris l'acide fumarique (TOVIAZ)

Title: Fésotérodine et ses sels avec des acides physiologiquement acceptables, y compris l'acide fumarique (TOVIAZ)
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: LU200791365C
Application Date: 2007-09-14
Publication Date: 2007-11-14
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: FR
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 28/45 SK286052B6 3,3-Diphenylpropylamines, pharmaceutical compositions, method for the preparation thereof and use

Title: 3,3-Diphenylpropylamines, pharmaceutical compositions, method for the preparation thereof and use
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: SK20001547A
Application Date: 1999-05-11
Publication Date: 2008-02-05
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
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A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762

C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
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A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122

A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222
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A61K0031315	A	A61	A61K	A61K0031	A61K0031315
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A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
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A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922

C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
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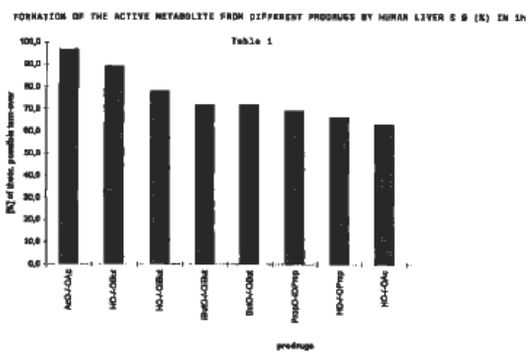
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Described are compounds of the formula (I) and (VII'), wherein the meaning of the substituents is described in description. Besides the method of the preparation of 3,3-diphenylpropylamines the pharmaceutical composition containing thereof is also described, that is active at treatment of urinary incontinence, gastrointestinal hyperactivity and other smooth muscle contractile conditions.
Language of Publication: SK
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 29/45 NL300293I2 Nieuwe derivaten van 3,3-difenylpropylaminen

Title: Nieuwe derivaten van 3,3-difenylpropylaminen
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A | EP1999924929A
Priority Date: 1998-05-12 | 1999-05-11 | 1999-05-11
Application Number: NL300293C
Application Date: 2007-09-13
Publication Date: 2008-03-03
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: NL
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 30/45 CA2328920C NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES | NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES | NOUVEAUX DERIVES DE 3,3-DIPHENYLPROPYLAMINES
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: CA2328920A
Application Date: 1999-05-11
Publication Date: 2008-04-15
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
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A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
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A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P004300	A	A61	A61P	A61P0043	A61P004300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
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C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
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A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216

A61K003122	A	A61	A61K	A61K0031	A61K003122
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A61K0031222	A	A61	A61K	A61K0031	A61K0031222
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A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
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C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762

C07C021922	C	C07	C07C	C07C0219	C07C021922
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C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
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C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARMA AG,MONHEIM,DE
JP F Terms:
JP FI Codes:
Assignee - Original: SCHWARZ PHARMA AG
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

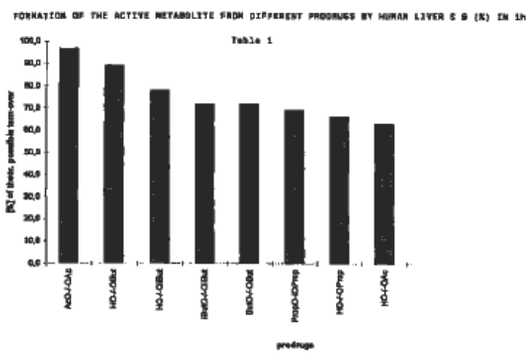
ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

L'invention concerne de nouveaux dérivés de 3,3-diphénylpropylamines, des procédés permettant de les préparer, des compositions pharmaceutiques contenant ces nouveaux composés et l'utilisation de ces composés pour la préparation de médicaments. L'invention concerne plus particulièrement de nouveaux précurseurs d'agents anti-muscariniques qui ont des propriétés pharmacocinétiques supérieures à celles des médicaments existants tels que l'oxybutynine et la toltérodine, un procédé de préparation de ces précurseurs, des compositions pharmaceutiques les contenant et un procédé d'utilisation de ces composés, ainsi que des compositions destinées au traitement de l'incontinence urinaire, de l'hyperactivité gastro-intestinale (syndrome du côlon irritable) et d'autres pathologies affectant la contractilité des muscles lisses.
Language of Publication: EN
INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2002-11-19	EEER	+
Description: EXAMINATION REQUEST		

Post-Issuance (US):
Reassignment (US) Table:

Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status: EX-RQ 2002-11-19 2002 Request for examination
Front Page Drawing:



Record 31/45 US7384980B2 Derivatives of 3,3-diphenylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A | US2001700094A | US2004766263A
Priority Date: 1998-05-12 | 1999-05-11 | 2001-01-02 | 2004-01-27
Application Number: US2005201756A
Application Date: 2005-08-10
Publication Date: 2008-06-10
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
A01N003712	A	A01	A01N	A01N0037	A01N003712
C12P001300	C	C12	C12P	C12P0013	C12P001300
A01N003744	A	A01	A01N	A01N0037	A01N003744
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A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
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A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
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C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
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C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
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A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222

A61K0031225	A	A61	A61K	A61K0031	A61K0031225
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K003124	A	A61	A61K	A61K0031	A61K003124
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A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928

C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
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C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
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C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
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C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: Schwarz Pharma AG,Monheim,DE
JP F Terms:
JP FI Codes:
Assignee - Original: Schwarz Pharma AG

Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2011-09-19	FPAY	+
Description: FEE PAYMENT		
2010-05-24	AS	-
Description: ASSIGNMENT UCB PHARMA GMBH, GERMANY CHANGE OF NAME; ASSIGNOR:SCHWARZ PHARMA AG; REEL/FRAME:024424/0724 2010-01-20		

Post-Issuance (US):

Reassignment (US) Table:

Assignee	Assignor	Date Signed	Reel/Frame	Date
UCB PHARMA GMBH,MONHEIM,DE	SCHWARZ PHARMA AG	2010-01-20	024424/0724	2010-05-24
Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).				
Corresponent: JEFFREY GINSBERG ONE BROADWAY KENYON & KENYON LLP NEW YORK, NY 10004				

Maintenance Status (US):

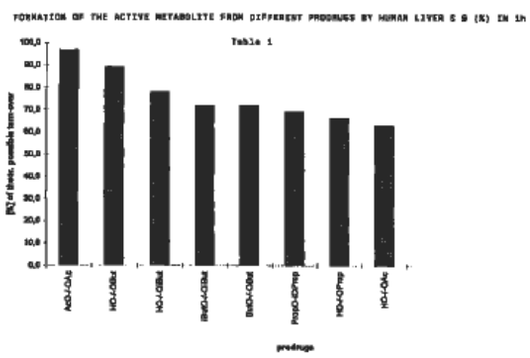
Litigation (US): 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Alkem Laboratories Ltd. Delaware 1:13cv01110 | 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Sandoz Inc. Delaware 1:13cv01111 | 2013-06-24 2013 Inc Pfizer UCB Pharma Gmbh Alkem Laboratories, Ltd. N.D. Illinois 1:13cv04628 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Accord Healthcare Inc., USA Delaware 1:13cv01155 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amerigen Pharmaceuticals Inc. Amerigen Pharmaceuticals Ltd Delaware 1:13cv01156 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amneal Pharmaceuticals LLC Delaware 1:13cv01157 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Impax Laboratories Inc. Delaware 1:13cv01158 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Lupin Ltd. Delaware 1:13cv01153 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Zydus Pharmaceuticals (USA) Inc. Delaware 1:13cv01154 | 2013-08-02 2013 Pfizer Inc. UCB Pharma Gmbh Wockhardt Bio AG Wockhardt USA LLC Delaware 1:13cv01387

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 32/45 GEP20084461B NEW DERIVATIVE OF 3,3- DIPHENYL-PROPYLAMINE

Title: NEW DERIVATIVE OF 3,3- DIPHENYL-PROPYLAMINE
Title - DWPI:
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: GE2007AP10260A
Application Date: 2007-09-10
Publication Date: 2008-08-25
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C000100	C	C07	C07C	C07C0001	C07C000100
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their pre¬para¬tion, pharmaceutical compositions containing them, and the use of the compounds for preparing antimuscarinic agents.
Language of Publication: EN
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 33/45 CZ299721B6 Medicament for treating urinary incontinence

Title: Medicament for treating urinary incontinence
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: CZ200629A
Application Date: 1999-05-11
Publication Date: 2008-10-29
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021928	C	C07	C07C	C07C0219	C07C021928
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
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A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
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A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
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A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
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C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222
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A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K003124	A	A61	A61K	A61K0031	A61K003124

A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
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A61K000970	A	A61	A61K	A61K0009	A61K000970
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A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
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C07C021922	C	C07	C07C	C07C0219	C07C021922
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C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
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C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
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C07C006922	C	C07	C07C	C07C0069	C07C006922
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C07H001518	C	C07	C07H	C07H0015	C07H001518
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C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office

Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

In the present invention, there is disclosed the use of (.+-.)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester, R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester or salt thereof with physiologically acceptable acids for the preparation of a medicament intended for the treatment of urinary incontinence.

Language of Publication: CS

INPADOC Legal Status Table:

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

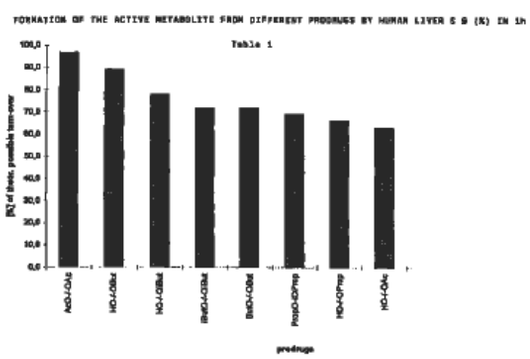
Litigation (US):

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 34/45 HU226490B1 NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES, PROCESS FOR PREPARING THEM, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND METHODS OF USE THEM

Title: NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES, PROCESS FOR PREPARING THEM, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND METHODS OF USE THEM
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: HU2001779A
Application Date: 1999-05-11
Publication Date: 2009-03-02
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C000100	C	C07	C07C	C07C0001	C07C000100
C12P001300	C	C12	C12P	C12P0013	C12P001300
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A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
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A61P000100	A	A61	A61P	A61P0001	A61P000100
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C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021900	C	C07	C07C	C07C0219	C07C021900

C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216

A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222
A61K0031225	A	A61	A61K	A61K0031	A61K0031225
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K003124	A	A61	A61K	A61K0031	A61K003124
A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762

C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

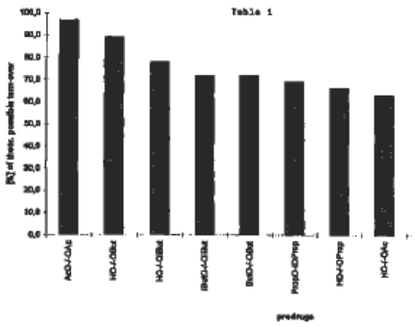
ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: HU
INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2010-12-28	FG4S	+
Description: GRANT OF SUPPLEMENTARY PROTECTION CERTIFICATE PRODUCT NAME: FESOTERODINE OPTIONALLY IN THE FORM OF PHARMACEUTICALLY ACCEPTABLE ACID ADDITION SALTINCLUDING FU ; REG. NO/DATE: EU/1/07/386/001-010 20070420		
2009-06-29	AA1S	+
Description: INFORMATION ON APPLICATION FOR A SUPPLEMENTARY PROTECTION CERTIFICATE PRODUCT NAME: FESOTERODINE OPTIONALLY IN THE FORM OF PHARMACEUTICALLY ACCEPTABLE ACID ADDITION SALTINCLUDING FU ; REG. NO/DATE: EU/1/07/386/001-010 20070420		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h

Table 1



Record 35/45 NO326872B1 Nye derivater av 3,3-difenylpropylaminer, farmasoytisk preparat inneholdende disse, samt fremgangsmater for fremstilling derav

Title: Nye derivater av 3,3-difenylpropylaminer, farmasoytisk preparat inneholdende disse, samt fremgangsmater for fremstilling derav
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: NO20005669A
Application Date: 2000-11-10
Publication Date: 2009-03-09
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021748	C	C07	C07C	C07C0217	C07C021748
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: NO
INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2012-11-12	SPCG	+
Description: GRANTED SUPPLEMENTARY PROTECTION CERTIFICATE PRODUCT NAME: TOVIAZ; NAT. REG. NO/DATE: EU107386001/NO-010/NO 20070531; FIRST REG. NO/DATE: EU107386001-010 20070420		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:

Front Page Drawing:

(No drawing/image available)

Record 36/45 CN100491336C Novel derivatives of 3,3-diphenylpropylamines

Title: Novel derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: CN200510070299A
Application Date: 1999-05-11
Publication Date: 2009-05-27
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021928	C	C07	C07C	C07C0219	C07C021928
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144

C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
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A61K0031222	A	A61	A61K	A61K0031	A61K0031222
A61K0031225	A	A61	A61K	A61K0031	A61K0031225
A61K0031235	A	A61	A61K	A61K0031	A61K0031235

A61K003124	A	A61	A61K	A61K0031	A61K003124
A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900

C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2011-05-18	C56	-
Description: CHANGE IN THE NAME OR ADDRESS OF THE PATENTEE UCB PHARMA INC. FORMER NAME: SCHWARZ PHARMA AG		
2011-05-18	C56	-
Description: CHANGE IN THE NAME OR ADDRESS OF THE PATENTEE		
2009-05-27	C14	+
Description: GRANTED		
2006-07-21	REG	-
Description: REFERENCE TO A NATIONAL CODE HK HK 1084099 DE REQUESTS TO DESIGNATE PATENT IN HONG KONG		
2005-12-28	C10	-
Description: REQUEST OF EXAMINATION AS TO SUBSTANCE		
2005-11-02	C06	+
Description: PUBLICATION		

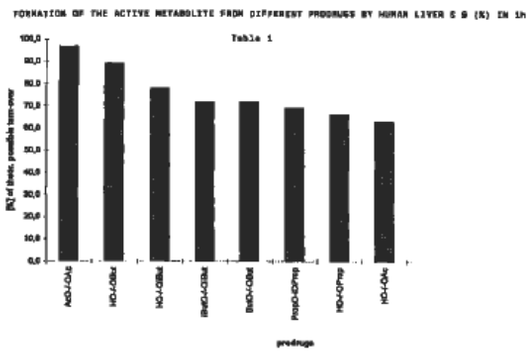
Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

Litigation (US):

Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 37/45 PL202489B1 Derivatives of 3,3-diphenylopropyloamines, their production methods, pharmaceutical composition and applications

Title: Derivatives of 3,3-diphenylopropyloamines, their production methods, pharmaceutical composition and applications
Title - DWPI:
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: PL380081A
Application Date: 1999-05-11
Publication Date: 2009-06-30
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021762	C	C07	C07C	C07C0217	C07C021762
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: PL
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 38/45 HK1084099A1 DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES 3,3-

Title: DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES 3,3-
Title - DWPI:
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: HK2006104367A
Application Date: 2006-04-11
Publication Date: 2009-11-20
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702

C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SANOL ARZNEI SCHWARZ GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		2013010120130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02			EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: ZH
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 39/45 DE122007000065I2 3,3-DIPHENYLPROPYLAMINDERIVATE

Title: 3,3-DIPHENYLPROPYLAMINDERIVATE
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: DE122007000065C
Application Date: 1999-05-11
Publication Date: 2010-03-25
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C000100	C	C07	C07C	C07C0001	C07C000100
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: SCHWARZ PHARMA AG ALFRED NOBEL
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: DE
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 40/45 US7855230B2 Derivatives of 3,3-diphenylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A | US2001700094A | US2004766263A | US2005201756A
Priority Date: 1998-05-12 | 1999-05-11 | 2001-01-02 | 2004-01-27 | 2005-08-10
Application Number: US2008105016A
Application Date: 2008-04-17
Publication Date: 2010-12-21
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
A61K003124	A	A61	A61K	A61K0031	A61K003124
C12P001300	C	C12	C12P	C12P0013	C12P001300
A01N003710	A	A01	A01N	A01N0037	A01N003710
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928

C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222

A61K0031225	A	A61	A61K	A61K0031	A61K0031225
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K003124	A	A61	A61K	A61K0031	A61K003124
A61K0031315	A	A61	A61K	A61K0031	A61K0031315
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928

C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: UCB Pharma GmbH,Monheim,DE
JP F Terms:
JP FI Codes:
Assignee - Original: UCB Pharma GmbH

Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

Language of Publication: EN

INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2010-05-18	AS	-
Description: ASSIGNMENT UCB PHARMA GMBH, GERMANY CHANGE OF NAME; ASSIGNOR:SCHWARZ PHARMA AG; REEL/FRAME:024400/0191 2010-01-20		

Post-Issuance (US):

Reassignment (US) Table:

Assignee	Assignor	Date Signed	Reel/Frame	Date
UCB PHARMA GMBH,MONHEIM,DE	SCHWARZ PHARMA AG	2010-01-20	024400/0191	2010-05-18
Conveyance: CHANGE OF NAME (SEE DOCUMENT FOR DETAILS).				
Corresponent: JEFFREY GINSBERG ONE BROADWAY KENYON & KENYON LLP NEW YORK, NY 10004				

Maintenance Status (US):

Litigation (US): 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Alkem Laboratories Ltd. Delaware 1:13cv01110 | 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Sandoz Inc. Delaware

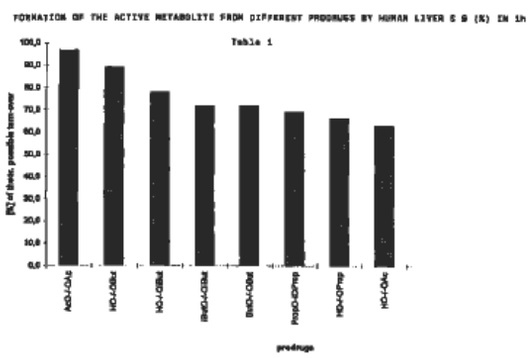
1:13cv01111 | 2013-06-24 2013 Inc Pfizer UCB Pharma Gmbh Alkem Laboratories, Ltd. N.D. Illinois 1:13cv04628 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Accord Healthcare Inc., USA Delaware 1:13cv01155 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amerigen Pharmaceuticals Inc. Amerigen Pharmaceuticals Ltd Delaware 1:13cv01156 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amneal Pharmaceuticals LLC Delaware 1:13cv01157 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Impax Laboratories Inc. Delaware 1:13cv01158 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Lupin Ltd. Delaware 1:13cv01153 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Zydus Pharmaceuticals (USA) Inc. Delaware 1:13cv01154 | 2013-08-02 2013 Pfizer Inc. UCB Pharma Gmbh Wockhardt Bio AG Wockhardt USA LLC Delaware 1:13cv01387

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



Record 41/45 JP04658895B2 The novel derivative of 3, 3- diphenylpropylamine

Title: The novel derivative of 3, 3- diphenylpropylamine
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: JP2006283861A
Application Date: 2006-10-18
Publication Date: 2011-03-23
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021748	C	C07	C07C	C07C0217	C07C021748
C12P001300	C	C12	C12P	C12P0013	C12P001300
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A61K0031222	A	A61	A61K	A61K0031	A61K0031222
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A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021300	C	C07	C07C	C07C0213	C07C021300

C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
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C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
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C07C030700	C	C07	C07C	C07C0307	C07C030700
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A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
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A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
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A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748

C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
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C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
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C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
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C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
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C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516

C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: SCHWARZ PHARMA AG,JP
JP F Terms: | 4B064AE01 | 4B064CA21 | 4B064DA01 | 4C022MA02 | 4C057BB02 | 4C057CC01 | 4C057DD02 | 4C057JJ20 | 4C086AA01 | 4C086AA02 | 4C086AA03 | 4C086BA17 | 4C086EA07 | 4C086MA01 | 4C086MA04 | 4C086MA09 | 4C086NA14 | 4C086ZA68 | 4C086ZA84 | 4C086ZA94 | 4C086ZC42 | 4C201 | 4C206AA01 | 4C206AA02 | 4C206AA03 | 4C206DB03 | 4C206DB04 | 4C206DB16 | 4C206DB29 | 4C206DB57 | 4C206JA06 | 4C206MA01 | 4C206MA16 | 4C206MA28 | 4C206NA14 | 4C206ZA68 | 4C206ZA84 | 4C206ZA94 | 4C206ZC42 | 4H006AA01 | 4H006AA02 | 4H006AA03 | 4H006AB20 | 4H006AB26 | 4H006AB84 | 4H006AC43 | 4H006AC48 | 4H006BB12 | 4H006BB15 | 4H006BB20 | 4H006BB31 | 4H006BB61 | 4H006BJ50 | 4H006BN30 | 4H006BP10 | 4H006BP30 | 4H006BT12 | 4H006BT16 | 4H006BU36
JP FI Codes: | A61K0031222 | A61K0031225 | A61K0031235 | A61K0031365 | A61K00317034 | A61P000104 | A61P001302 | A61P002100 | A61P004300-111 | C07B005300-G | C07C021300 | C07C021306 | C07C021748 | C07C021922 | C07C021928 | C07D032100 | C07H001518 | C12P001300
Assignee - Original: SCHWARZ PHARMA AG
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: JA
INPADOC Legal Status Table:

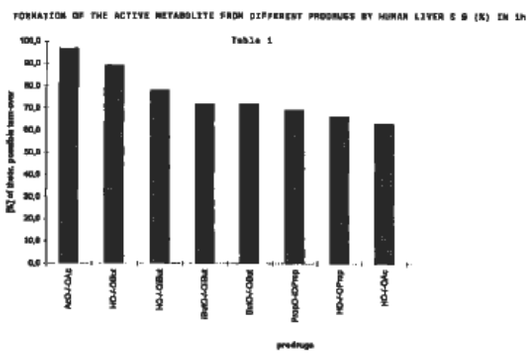
Gazette Date	Code	INPADOC Legal Status Impact
2011-04-13	RD04	-
Description: NOTIFICATION OF RESIGNATION OF POWER OF ATTORNEY JAPANESE INTERMEDIATE CODE: R3D04		
2011-04-13	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140107		
2011-03-28	RD02	-

Description: NOTIFICATION OF ACCEPTANCE OF POWER OF ATTORNEY JAPANESE INTERMEDIATE CODE: R3D02		
2011-02-10	R350	-
Description: WRITTEN NOTIFICATION OF REGISTRATION OF TRANSFER JAPANESE INTERMEDIATE CODE: R350		
2011-02-10	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140107		
2011-02-02	S533	-
Description: WRITTEN REQUEST FOR REGISTRATION OF CHANGE OF NAME JAPANESE INTERMEDIATE CODE: R313533		
2011-02-02	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140107		
2011-01-07	R150	+
Description: CERTIFICATE OF PATENT (=GRANT) OR REGISTRATION OF UTILITY MODEL JAPANESE INTERMEDIATE CODE: R150		
2011-01-07	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140107		
2011-01-06	A61	+
Description: FIRST PAYMENT OF ANNUAL FEES (DURING GRANT PROCEDURE) JAPANESE INTERMEDIATE CODE: A61 2010-12-24		
2010-12-16	A01	+
Description: WRITTEN DECISION TO GRANT A PATENT OR TO GRANT A REGISTRATION (UTILITY MODEL) JAPANESE INTERMEDIATE CODE: A01		
2010-12-09	A01	+
Description: WRITTEN DECISION TO GRANT A PATENT OR TO GRANT A REGISTRATION (UTILITY MODEL) JAPANESE INTERMEDIATE CODE: A01 2010-12-08		
2010-12-01	TRDD	+

Description: DECISION OF GRANT OR REJECTION WRITTEN		
2010-11-18	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2010-11-17		
2010-10-15	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2010-10-14		
2010-10-09	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2010-10-08		
2010-09-27	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2010-09-24		
2010-09-18	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2010-09-17		
2010-08-19	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2010-08-18		
2010-08-14	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2010-08-13		
2010-05-20	A131	-
Description: NOTIFICATION OF REASONS FOR REFUSAL JAPANESE INTERMEDIATE CODE: A131 2010-05-19		
2007-02-28	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2007-02-27		
2006-12-27	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2006-11-30		

Post-Issuance (US):
Reassignment (US) Table:

Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 42/45 US7985772B2 Derivatives of 3,3-diphenylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A | US2001700094A | US2004766263A | US2005201756A | US2008105016A
Priority Date: 1998-05-12 | 1999-05-11 | 2001-01-02 | 2004-01-27 | 2005-08-10 | 2008-04-17
Application Number: US2010814982A
Application Date: 2010-06-14
Publication Date: 2011-07-26
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
A61K003121	A	A61	A61K	A61K0031	A61K003121
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
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C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762

C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
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C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
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A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
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A61K003122	A	A61	A61K	A61K0031	A61K003122

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A61K0031235	A	A61	A61K	A61K0031	A61K0031235
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A61P002502	A	A61	A61P	A61P0025	A61P002502
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C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922

C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
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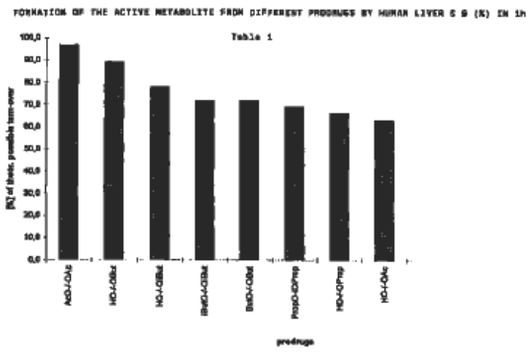
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516
C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: UCB Pharma GmbH,Monheim,DE
JP F Terms:
JP FI Codes:
Assignee - Original: UCB Pharma GmbH
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
The invention concerns novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.
Language of Publication: EN
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US): 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Alkem Laboratories Ltd. Delaware 1:13cv01110 | 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Sandoz Inc. Delaware 1:13cv01111 | 2013-06-24 2013 Inc Pfizer UCB Pharma Gmbh Alkem Laboratories, Ltd. N.D. Illinois 1:13cv04628 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Accord Healthcare Inc., USA Delaware 1:13cv01155 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amerigen Pharmaceuticals Inc. Amerigen Pharmaceuticals Ltd Delaware 1:13cv01156 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amneal Pharmaceuticals LLC Delaware 1:13cv01157 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Impax Laboratories Inc. Delaware 1:13cv01158 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Lupin Ltd. Delaware 1:13cv01153 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Zydus Pharmaceuticals (USA) Inc. Delaware 1:13cv01154 | 2013-08-02 2013 Pfizer Inc. UCB Pharma Gmbh Wockhardt Bio AG Wockhardt USA LLC Delaware 1:13cv01387
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 43/45 JP04833884B2 The novel derivative|guide_body of 3, 3- diphenylpropylamine

Title: The novel derivative|guide_body of 3, 3- diphenylpropylamine
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A
Priority Date: 1998-05-12
Application Number: JP200739857A
Application Date: 2007-02-20
Publication Date: 2011-12-07
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C07C021930	C	C07	C07C	C07C0219	C07C021930
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108

C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
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C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
A61K0031215	A	A61	A61K	A61K0031	A61K0031215
A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P002502	A	A61	A61P	A61P0025	A61P002502

IPC Class Table - DWPI:

IPC - DWPI	Section - DWPI	Class - DWPI	Subclass - DWPI	Class Group - DWPI	Subgroup - DWPI
C07C021700	C	C07	C07C	C07C0217	C07C021700
C07C021900	C	C07	C07C	C07C0219	C07C021900
C07C027100	C	C07	C07C	C07C0271	C07C027100
C07C030700	C	C07	C07C	C07C0307	C07C030700
A01N003702	A	A01	A01N	A01N0037	A01N003702
A01N003706	A	A01	A01N	A01N0037	A01N003706
A01N003710	A	A01	A01N	A01N0037	A01N003710
A01N003712	A	A01	A01N	A01N0037	A01N003712
A01N003744	A	A01	A01N	A01N0037	A01N003744
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031137	A	A61	A61K	A61K0031	A61K0031137
A61K003121	A	A61	A61K	A61K0031	A61K003121
A61K0031215	A	A61	A61K	A61K0031	A61K0031215

A61K0031216	A	A61	A61K	A61K0031	A61K0031216
A61K003122	A	A61	A61K	A61K0031	A61K003122
A61K0031221	A	A61	A61K	A61K0031	A61K0031221
A61K0031222	A	A61	A61K	A61K0031	A61K0031222
A61K0031225	A	A61	A61K	A61K0031	A61K0031225
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A61K003124	A	A61	A61K	A61K0031	A61K003124
A61K0031315	A	A61	A61K	A61K0031	A61K0031315
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A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
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A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61K00317034	A	A61	A61K	A61K0031	A61K00317034
A61K000970	A	A61	A61K	A61K0009	A61K000970
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P000104	A	A61	A61P	A61P0001	A61P000104
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001302	A	A61	A61P	A61P0013	A61P001302
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P002100	A	A61	A61P	A61P0021	A61P002100
A61P002502	A	A61	A61P	A61P0025	A61P002502
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07B005300	C	C07	C07B	C07B0053	C07B005300
C07C000100	C	C07	C07C	C07C0001	C07C000100
C07C021100	C	C07	C07C	C07C0211	C07C021100
C07C021300	C	C07	C07C	C07C0213	C07C021300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748

C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021926	C	C07	C07C	C07C0219	C07C021926
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C021930	C	C07	C07C	C07C0219	C07C021930
C07C022900	C	C07	C07C	C07C0229	C07C022900
C07C023347	C	C07	C07C	C07C0233	C07C023347
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152
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C07C0069017	C	C07	C07C	C07C0069	C07C0069017
C07C006922	C	C07	C07C	C07C0069	C07C006922
C07C006934	C	C07	C07C	C07C0069	C07C006934
C07C006976	C	C07	C07C	C07C0069	C07C006976
C07C006978	C	C07	C07C	C07C0069	C07C006978
C07D020706	C	C07	C07D	C07D0207	C07D020706
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518
C12P001300	C	C12	C12P	C12P0013	C12P001300
C07C021546	C	C07	C07C	C07C0215	C07C021546
A61K0031395	A	A61	A61K	A61K0031	A61K0031395
C07C021754	C	C07	C07C	C07C0217	C07C021754
C07C022902	C	C07	C07C	C07C0229	C07C022902
C07C027140	C	C07	C07C	C07C0271	C07C027140
C07C030704	C	C07	C07C	C07C0307	C07C030704
C07D029516	C	C07	C07D	C07D0295	C07D029516

C07F000708	C	C07	C07F	C07F0007	C07F000708

Assignee/Applicant: UCB PHARMA GMBH,JP
JP F Terms: | 4C201 | 4C206AA01 | 4C206AA02 | 4C206AA03 | 4C206AA04 | 4C206FA11 | 4C206GA02 | 4C206GA28 | 4C206MA01 | 4C206MA04 | 4C206NA14 | 4C206ZA24 | 4C206ZA66 | 4C206ZA81 | 4C206ZA84 | 4H006AA01 | 4H006AA02 | 4H006AA03 | 4H006AB20 | 4H006BJ50 | 4H006BN10 | 4H006BT16 | 4H006BU32
JP FI Codes: | A61K0031215 | A61K0031216 | A61K0031221 | A61K0031325 | A61P000100 | A61P001302 | A61P002502-103 | C07C021306 | C07C021930 | C07C023347 | C07C027144
Assignee - Original: UCB PHARMA GMBH
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

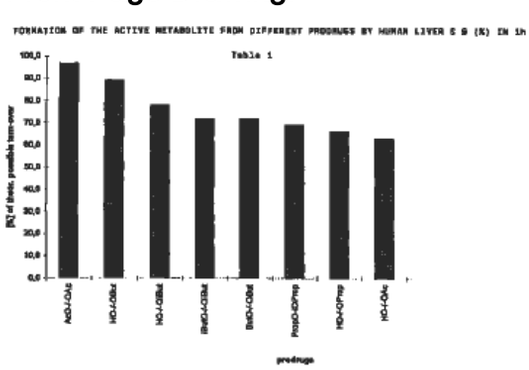
ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: JA
INPADOC Legal Status Table:

Gazette Date	Code	INPADOC Legal Status Impact
2011-10-03	FPAY	+
Description: RENEWAL FEE PAYMENT (PRS DATE IS RENEWAL DATE OF DATABASE) PAYMENT UNTIL: 20140930		
2011-09-30	R150	+
Description: CERTIFICATE OF PATENT (=GRANT) OR REGISTRATION OF UTILITY MODEL JAPANESE INTERMEDIATE CODE: R150		
2011-09-29	A61	+
Description: FIRST PAYMENT OF ANNUAL FEES (DURING GRANT PROCEDURE) JAPANESE INTERMEDIATE CODE: A61 2011-09-22		
2011-09-08	A01	+
Description: WRITTEN DECISION TO GRANT A PATENT OR TO GRANT A REGISTRATION (UTILITY MODEL) JAPANESE INTERMEDIATE CODE: A01		

2011-09-05	A01	+
Description: WRITTEN DECISION TO GRANT A PATENT OR TO GRANT A REGISTRATION (UTILITY MODEL) JAPANESE INTERMEDIATE CODE: A01 2011-09-02		
2011-08-31	TRDD	+
Description: DECISION OF GRANT OR REJECTION WRITTEN		
2011-04-23	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2011-04-22		
2011-04-09	RD04	-
Description: NOTIFICATION OF RESIGNATION OF POWER OF ATTORNEY JAPANESE INTERMEDIATE CODE: A7424 2011-04-08		
2011-03-28	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2011-03-25		
2011-03-23	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2011-03-22		
2011-02-16	RD02	-
Description: NOTIFICATION OF ACCEPTANCE OF POWER OF ATTORNEY JAPANESE INTERMEDIATE CODE: A7422 2011-01-27		
2010-12-24	A131	-
Description: NOTIFICATION OF REASONS FOR REFUSAL JAPANESE INTERMEDIATE CODE: A131 2010-12-22		
2010-12-03	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2010-12-02		
2010-11-18	A521	-
Description: WRITTEN AMENDMENT JAPANESE INTERMEDIATE CODE: A523 2010-11-17		
2010-10-15	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2010-10-14		

2010-10-09	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2010-10-08		
2010-09-27	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2010-09-24		
2010-09-18	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2010-09-17		
2010-08-18	A602	-
Description: WRITTEN PERMISSION OF EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A602 2010-08-17		
2010-08-13	A601	-
Description: WRITTEN REQUEST FOR EXTENSION OF TIME JAPANESE INTERMEDIATE CODE: A601 2010-08-12		
2010-05-20	A131	-
Description: NOTIFICATION OF REASONS FOR REFUSAL JAPANESE INTERMEDIATE CODE: A131 2010-05-19		

Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:



Record 44/45 NO2009015I2 Fesoterodine, eventuelt i form av et fysiologisk akseptabelt salt, inkludert hydrogenfumaratsaltet

Title: Fesoterodine, eventuelt i form av et fysiologisk akseptabelt salt, inkludert hydrogenfumaratsaltet
Title - DWPI:
Priority Number: EP1998108608A | WO1999EP3212A
Priority Date: 1998-05-12 | 1999-05-11
Application Number: NO200915C
Application Date: 2009-07-17
Publication Date: 2012-11-12
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
A61K0031365	A	A61	A61K	A61K0031	A61K0031365
A61K003140	A	A61	A61K	A61K0031	A61K003140
A61K0031435	A	A61	A61K	A61K0031	A61K0031435
A61K00317028	A	A61	A61K	A61K0031	A61K00317028
A61P000100	A	A61	A61P	A61P0001	A61P000100
A61P001300	A	A61	A61P	A61P0013	A61P001300
A61P001310	A	A61	A61P	A61P0013	A61P001310
A61P004300	A	A61	A61P	A61P0043	A61P004300
C07C021306	C	C07	C07C	C07C0213	C07C021306
C07C021748	C	C07	C07C	C07C0217	C07C021748
C07C021762	C	C07	C07C	C07C0217	C07C021762
C07C021922	C	C07	C07C	C07C0219	C07C021922
C07C021928	C	C07	C07C	C07C0219	C07C021928
C07C027108	C	C07	C07C	C07C0271	C07C027108
C07C027144	C	C07	C07C	C07C0271	C07C027144
C07C027152	C	C07	C07C	C07C0271	C07C027152

C07C030702	C	C07	C07C	C07C0307	C07C030702
C07D029506	C	C07	C07D	C07D0295	C07D029506
C07D032100	C	C07	C07D	C07D0321	C07D032100
C07D032110	C	C07	C07D	C07D0321	C07D032110
C07F000718	C	C07	C07F	C07F0007	C07F000718
C07H001518	C	C07	C07H	C07H0015	C07H001518

IPC Class Table - DWPI:
Assignee/Applicant: UCB PHARMA GMBH
JP F Terms:
JP FI Codes:
Assignee - Original:
Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702
Abstract:
Language of Publication: NO
INPADOC Legal Status Table:
Post-Issuance (US):
Reassignment (US) Table:
Maintenance Status (US):
Litigation (US):
Opposition (EP):
License (EP):
EPO Procedural Status:
Front Page Drawing:

(No drawing/image available)

Record 45/45 US8338478B2 Derivatives of 3,3-diphenylpropylamines

Title: Derivatives of 3,3-diphenylpropylamines
Title - DWPI: New diphenyl-propylamine derivatives useful as antimuscarinic agents for treatment of e.g. urinary incontinence and irritable bowel syndrome
Priority Number: EP1998108608A | WO1999EP3212A | US2001700094A | US2004766263A | US2005201756A | US2008105016A | US2010814982A
Priority Date: 1998-05-12 | 1999-05-11 | 2001-01-02 | 2004-01-27 | 2005-08-10 | 2008-04-17 | 2010-06-14
Application Number: US13161049A
Application Date: 2011-06-15
Publication Date: 2012-12-25
IPC Class Table:

IPC	Section	Class	Subclass	Class Group	Subgroup
A61K003121	A	A61	A61K	A61K0031	A61K003121
C12P001300	C	C12	C12P	C12P0013	C12P001300
A61K0031135	A	A61	A61K	A61K0031	A61K0031135
A61K0031235	A	A61	A61K	A61K0031	A61K0031235
A61K0031325	A	A61	A61K	A61K0031	A61K0031325
A61K0031357	A	A61	A61K	A61K0031	A61K0031357
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A61K003140	A	A61	A61K	A61K0031	A61K003140
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IPC Class Table - DWPI:

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Assignee/Applicant: UCB Pharma GmbH,Monheim,DE
JP F Terms:
JP FI Codes:
Assignee - Original: UCB Pharma GmbH

Any CPC Table:

Type	Invention	Additional	Version	Office
Current	C07C 217/48	-	20130101	EP
Current	C07C 217/62		20130101	EP
Current	C07C 219/28		20130101	EP
Current	C07C 229/34		20130101	EP
Current	C07C 271/44		20130101	EP
Current	C07C 271/52		20130101	EP
Current	C07C 307/02		20130101	EP

ECLA: C07C021748 | C07C021762 | C07C021928 | C07C022934 | C07C027144 | C07C027152 | C07C030702

Abstract:

The invention concerns novel derivatives of 3,3-diphenyl-propylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compounds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

Language of Publication: EN

INPADOC Legal Status Table:

Post-Issuance (US):

Reassignment (US) Table:

Maintenance Status (US):

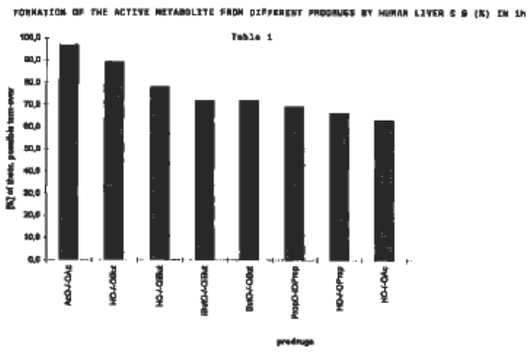
Litigation (US): 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Alkem Laboratories Ltd. Delaware 1:13cv01110 | 2013-06-21 2013 Pfizer Inc. UCB Pharma Gmbh Sandoz Inc. Delaware 1:13cv01111 | 2013-06-24 2013 Inc Pfizer UCB Pharma Gmbh Alkem Laboratories, Ltd. N.D. Illinois 1:13cv04628 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Accord Healthcare Inc., USA Delaware 1:13cv01155 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amerigen Pharmaceuticals Inc. Amerigen Pharmaceuticals Ltd Delaware 1:13cv01156 35 USC 271 Patent Infringement ::: ## | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Amneal Pharmaceuticals LLC Delaware 1:13cv01157 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Impax Laboratories Inc. Delaware 1:13cv01158 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Lupin Ltd. Delaware 1:13cv01153 | 2013-06-28 2013 Pfizer, Inc. UCB Pharma Gmbh Zydus Pharmaceuticals (USA) Inc. Delaware 1:13cv01154 | 2013-08-02 2013 Pfizer Inc. UCB Pharma Gmbh Wockhardt Bio AG Wockhardt USA LLC Delaware 1:13cv01387

Opposition (EP):

License (EP):

EPO Procedural Status:

Front Page Drawing:



USPTO Maintenance Report

Patent Bibliographic Data					09/17/2013 03:56 PM
Patent Number:	6713464		Application Number:	09700094	
Issue Date:	03/30/2004		Filing Date:	01/02/2001	
Title:	NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES				
Status:	12th year fee window opens: 03/30/2015			Entity:	LARGE
Window Opens:	N/A	Surcharge Date:	N/A	Expiration:	N/A
Fee Amt Due:	Window not open	Surchg Amt Due:	Window not open	Total Amt Due:	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	08/31/2011 09/07/2007	Payment of Maintenance Fee, 8th Year, Large Entity. Payment of Maintenance Fee, 4th Year, Large Entity. --- End of Maintenance History ---			
Address for fee purposes:	EDWARDS WILDMAN PALMER LLP P.O. BOX 55874 BOSTON MA 02205				